The New England
Journal of Medicine

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Volume 255 SEPTEMBER 6, 1956 Number 10

METALLOENZYMES AND MYOCARDIAL INFARCTION*

II. Malic and Lactic Dehydrogenase Activities and Zinc Concentrations in Serum

WARREN E. C. WACKER, M.D.,† DAVID D. ULMER, M.D.,‡ AND BERT L. VALLEE, M.D.§

BOSTON

PREVIOUS studies in this laboratory have shown that the concentration of copper in serum is considerably increased after acute myocardial infarction.[1] This change is proportional to an increase in ceruloplasmin, the copper protein of human serum, and its capacity to oxidize paraphenylenediamine.[2] In the pursuit of these studies, the concentration of zinc and the activity of zinc enzymes in human serum have been found to be altered markedly in myocardial necrosis.

Lactic dehydrogenase has recently been shown to be a zinc enzyme,[3] and malic dehydrogenase also appears to be a metalloenzyme.[4] These enzymes require coenzyme 1 (diphosphopyridine nucleotide) for their activity, as do alcohol and glutamic dehydrogenase, previously shown to be zinc metalloenzymes.[5,6] Malic and lactic dehydrogenases, like the metabolic products that they oxidize and reduce, are distributed throughout the body tissues, although heart muscle has been used as the primary source for purification and isolation in mammals.[7-12] Normal human serum oxidizes malate and lactate; it does not oxidize ethanol or glutamic acid.

The present study demonstrates a significant *decrease* of zinc concentration and an *increase* in malic and lactic dehydrogenase activity of human serum after acute myocardial infarction. These changes occur early in the course of the disease and are so characteristic and marked that they have proved to be valuable adjuvants to the diagnosis of myocardial infarction.

*From the Biophysics Research Laboratory and the Medical Clinic, Harvard Medical School and Peter Bent Brigham Hospital.

Supported by a contract between the Office of Naval Research and Harvard Medical School (Contract No. NR 119-277) and grants-in-aid from the John A. Hartford Foundation and the Howard Hughes Medical Institute.

†Research fellow, Harvard Medical School; junior associate in medicine, Peter Bent Brigham Hospital; fellow of the National Foundation for Infantile Paralysis.

‡Assistant resident in medicine, Peter Bent Brigham Hospital.

§Assistant professor of medicine, Harvard Medical School; senior associate in medicine, Peter Bent Brigham Hospital; research associate, Massachusetts Institute of Technology.

MATERIAL

Twenty-one healthy adults, 11 males and 10 females, ranging in age from nineteen to fifty-nine years, served as controls for malic dehydrogenase activity; 42 healthy adults, 21 males and 21 females, nineteen to fifty-nine years of age, served as controls for serum lactic dehydrogenase activity. All subjects were ambulatory, and the enzyme activities were determined without regard to the intake of food or physical exertion. Strenuous exercise, such as bicycle riding for thirty minutes, had no effect on serum lactic dehydrogenase activity in a healthy male volunteer.

Twenty-three patients, 9 males and 14 females, ranging in age from nineteen to eighty-seven years and hospitalized for a wide variety of clinical conditions, were also studied for serum lactic dehydrogenase activity. The patients included in this group suffered from renal disease with uremia, hypertensive cardiovascular and inactive rheumatic heart disease, cerebrovascular accidents, pulmonary infarction, lymphoma, gangrene, cholecystitis and endocrine disease; none had recently undergone acute myocardial infarction.

Serial determinations of serum lactic dehydrogenase activity were obtained on 22 patients who had sustained an unquestionable acute myocardial infarction. These 13 males and 9 females ranged in age from thirty-three to eighty-four years. There were 5 deaths in this group and post-mortem examination, performed in 2 cases, confirmed the clinical diagnosis.

Serum malic dehydrogenase activity was similarly determined in 7 patients, 6 males and 1 female, ranging in age from fifty-three to sixty-seven years. Post-mortem examination confirmed the diagnosis of acute myocardial infarction in the 1 fatal case of this group.

Serum zinc was determined in 8 patients, 6 males and 2 females, whose ages ranged from fifty-two to seventy-eight years. Four of these patients died. The clinical diagnosis could be confirmed in 2 pa-

tients for whom post-mortem examination was permitted.

In all cases acute myocardial infarction was diagnosed on the basis of history, characteristic sequential electrocardiographic changes, elevation of the leukocyte count, erythrocyte sedimentation rate and temperature and sudden appearance of congestive heart failure, friction rub or gallop rhythm. Patients were not included in the series unless the diagnosis was considered unequivocal on the basis of the characteristic criteria mentioned above. The presumable time of infarction was estimated by the time of occurrence of chest pain, syncope, dyspnea or vomiting. The group was studied sequentially, as admitted to the hospital over a period of four months. The clinical courses varied considerably. Whereas 11 patients experienced an uneventful recovery, 11 cases were complicated by congestive heart failure, severe hypotension, pulmonary and visceral emboli or pneumonia.

Sixteen patients, 12 males and 4 females, from forty-five to eighty-nine years of age, admitted to the hospital with a diagnosis of suspected acute myocardial infarction, were also studied. All gave a history compatible with acute myocardial infarction, but none exhibited diagnostic electrocardiographic changes at the time of admission when the enzymatic activity of the serum was first determined. They will be discussed as a separate group.

Methods

Both malic and lactic dehydrogenase activity was measured spectrophotometrically by the technic proposed by Warburg, Christian and Griese[14] and von Euler et al.,[15,16] based on the characteristic absorption of radiation of 340 millimicrons by diphosphopyridine-nucleotide-hydrogenase-reduced coenzyme 1. At this wave length, the oxidized coenzyme does not absorb light; any dehydrogenation reaction, dependent on this coenzyme, may be followed spectrophotometrically by virtue of the appearance or disappearance of reduced diphosphopyridine nucleotide.*

Malic Dehydrogenase

Sodium phosphate buffer, 0.3 ml. (0.2 molar, pH 7.4), reduced diphosphopyridine nucleotide, 0.2 ml. (0.003 molar, pH 7.0), 2.2 ml. of distilled water and 0.2 ml. of serum are mixed in a 3-ml. Beckman cuvette of 1-cm. path length. The mixture stands for twenty minutes at room temperature, and 0.1 ml. of 0.0076 molar oxaloacetate, pH 7.4, is then added. The reduction of diphosphopyridine nucleotide hydrogenase, as evidenced by a decrease in absorption at 340 millimicrons, is followed in the Beckman spectrophotometer against a "blank" consisting of 0.2 ml. of serum and 2.8 ml. of distilled water. The slit width is adjusted to 0.6 mm. Sequential readings are obtained every fifteen seconds for a total period of two minutes. The oxidation of reduced diphosphopyridine nucleotide yields a proton to produce malate from oxaloacetate; therefore, the *rate* of disappearance of the coenzyme is equivalent to the production of malate. One unit of malic dehydrogenase activity is defined as a decrease in the optical density at 340 millimicrons of 0.001 per minute per milliliter of serum.

Lactic Dehydrogenase

Sodium phosphate buffer, 1.5 ml. (0.1 molar, pH 8.8), 1.0 ml. of sodium lactate (0.16 molar, pH 7.0) and 0.3 ml. of diphosphopyridine nucleotide (0.05 molar, pH 7.5) are mixed in a 3-ml. Beckman cuvette of 1-cm. path length. Just before the cuvette is placed

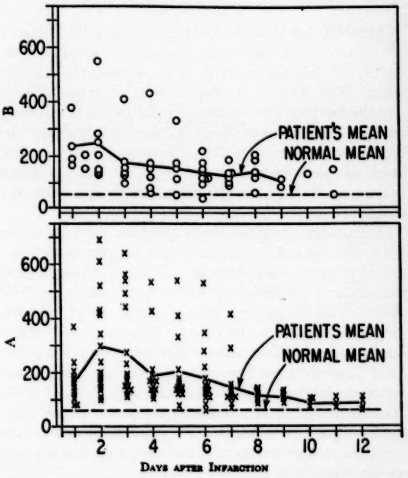

Figure 1. *Time Course of Serum Lactic Dehydrogenase Activity in 22 Patients* (A) *and Serum Malic Dehydrogenase Activity in 7 Patients* (B) *with Acute Myocardial Infarction. Enzyme units: 1 MDH or LDH unit = change of optical density per minute per milliliter of serum.*

in the spectrophotometer, 0.2 ml. of serum is rapidly added to the reaction mixture. The rate of appearance of reduced diphosphopyridine nucleotide at 340 millimicrons is examined at a slit width of 0.6 mm. against a "blank" consisting of 0.3 ml. of the coenzyme and 2.7 ml. of distilled water. Readings are recorded every thirty seconds for three minutes. The reduction of the coenzyme, reduced diphosphopyridine nucleotide removes a proton from lactic acid yielding pyruvic acid; therefore, the rate of appearance of the reduced coenzyme is equivalent to the disappearance of lactic acid. One unit of lactic dehydrogenase activity is defined as an increase in

*These spectral changes are also utilized in the determination of serum glutamico oxaloacetic transaminase activity, which has been shown to rise after acute myocardial infarction.[17,18]

optical density at 340 millimicrons of 0.001 per minute per milliliter of serum.

Procedure

Venous blood was obtained without regard to the fasting state. Malic dehydrogenase and zinc were determined daily or less often on four patients. Lactic dehydrogenase was determined at eight-hour intervals. After clotting, samples were centrifuged and the serum decanted and stored at 4°C. Determinations were generally carried out within forty-eight hours. Storage of the serum at 4°C. for ten days had no significant effect on the enzymatic activity.

Serum zinc concentration was measured microchemically in duplicate by means of the dithizone method of Hoch and Vallee.[18]

Statistical Method

The study of serum zinc concentrations in patients with acute myocardial infarction was guided by the sequential probability ratio test, which has been described and applied elsewhere.[19-21]

Results

The reproducibility of the lactic dehydrogenase method is excellent. The mean for repeated determinations upon the same serum sample of a normal subject was 50 units ± 4.34* lactic dehydrogenase (LDH) units.

The serum malic dehydrogenase activity of 21 healthy adults ranged from 40 to 80, with a mean of 57 ± 11 malic dehydrogenase (MDH) units.

The serum lactic dehydrogenase activity of 42 healthy adults ranged from 25 to 100, with a mean of 59 ± 19 LDH units. The 23 patients hospitalized with disease other than acute myocardial infarction exhibited serum activity from 40 to 115 LDH units, with a mean = 69 ± 20, indicating no statistically significant difference between this and the normal group.

Serum lactic dehydrogenase activity in each of the 22 patients with proved myocardial infarction was elevated two to ten times above the normal range. A scattergram compares the determinations on these patients with the mean ± 2 standard deviations of the normal group (Fig. 1A). The solid line represents the daily mean of all determinations on the experimental subjects.

Serum was obtained on 10 of these patients on the first day on which myocardial infarction was assumed to have been sustained. In 2 of these cases, the first determination was within the normal range,—that is, 80 units, — but a subsequent determination later during the same day was elevated in 1 of the 2 and a day later in the second patient. Two cases presented only slightly elevated activity, 105 to 110 LDH units respectively. The other 6 patients had markedly elevated activities ranging from 130 to 370 LDH units.

Twelve patients were sampled on the second day, and activity was elevated in all 12, ranging from 110 to 610 LDH units — the lowest value being that of a patient whose activity was 205 LDH units on the first day.

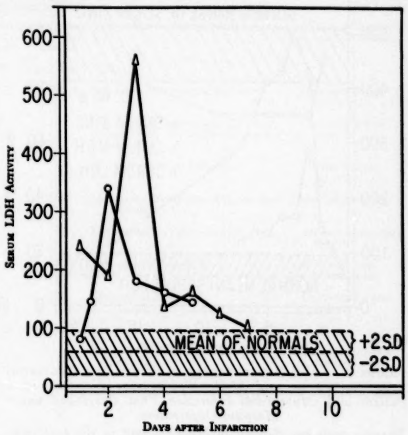

FIGURE 2. *Serial Determinations of Serum Lactic Dehydrogenase Activity in 2 Typical Patients with Acute Myocardial Infarction.*

Enzyme units: 1 LDH unit = change of optical density per minute per milliliter of serum.

Twelve patients were sampled on the third day, and all exhibited activity ranging from 115 to 640 LDH units; 6 patients of this group had activity higher than 225 units.

Activity remained elevated in all cases tested on the fourth day. By the fifth day, it had returned to normal in only 1 case and by the sixth day in 2 additional cases. In the remaining cases, activity returned to normal levels between the seventh and eleventh days.

The enzymatic activity of 2 typical patients is shown in Figure 2. The maximal activities occurred on the second and third days, with a steady decline to normal levels thereafter. There was no consistently demonstrable correlation between activity on the one hand and white-cell count, temperature or erythrocyte sedimentation rate on the other.

The type of data available and the number of cases studied preclude significant correlation between the severity of myocardial infarction as judged clinically, and the serum lactic dehydrogenase activity.

*All data are expressed as the mean, m, ± 1 standard deviation (S.D.). The S.D. was calculated as $\text{S.D.} = \sqrt{\frac{(d)^2}{n-1}}$ where d = deviation from the mean and n = number of observations.

It was observed, however, that 2 of the patients who succumbed to their disease exhibited the most persistently high elevations of activity observed in this series.

Complications in some cases caused a secondary rise of activity and delayed its return to normal. One patient sustained a renal infarction, presumably embolic, on the seventh day of hospitalization, accompanied by a secondary rise of activity. In another patient a friction rub developed on the eighth day, with a recurrent elevation of the value from 110 to 135 LDH units. Clinical extension of infarction, as judged by recurrent chest pain and tachycardia with or without fever, was sometimes — but not uniformly — associated with a break in the usual downward trend of the serum-activity curve.

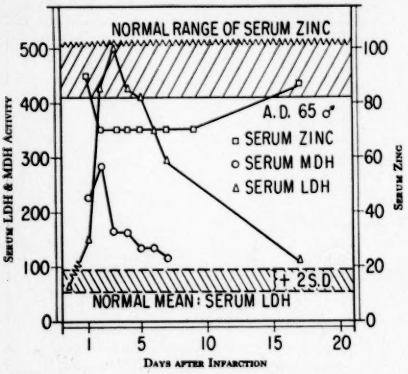

FIGURE 3. *Serial Determinations of Serum Zinc Concentrations and Lactic and Malic Hydrogenase Activities in a Patient with Myocardial Infarction That Developed under Hospital Observation.*

Enzyme units are defined in Figure 1 and in the text; zinc concentrations are given in micrograms of zinc per 100 ml. of serum. (Note that the lactic dehydrogenase activities are higher than the malic dehydrogenase activities in this patient.)

Sixteen patients were admitted to the hospital with a diagnosis of *suspected* acute myocardial infarction. Three of these, who are included in the composite graph (Fig. 1), were admitted to the hospital because of chest pain, suggestive of myocardial infarction. The initial electrocardiograms did not show acute myocardial infarction and other evidences of myocardial necrosis were absent. Serum lactic dehydrogenase activity was normal on admission. These 3 patients each experienced recurrent chest pain accompanied by definite clinical and electrocardiographic evidence of myocardial infarction three to six days after admission. The serum activity rose promptly in each. Figure 3 presents the data in 1 of these 3 cases and shows the characteristic rise of both lactic and malic dehydrogenase. The remaining 13 cases are summarized in Table 1. Ten of these patients were not considered to have sustained acute myocardial infarction on the basis of the clinical course and laboratory data. The lactic dehydrogenase values were normal in 7 of these patients, ranging from 30 to 95 units on one or more determinations. Three of this group (Cases 8, 9 and 10) exhibited activities up to 115 LDH units in 2 cases and 130 units in the other. The remaining 3 cases (Cases 11, 12 and 13) in this series of 16 were diagnosed at discharge as probable acute myocardial infarction on the basis of the history and clinical course. Activity remained at or below 110 LDH units in 2 cases and reached 120 units in the third. None of these 3 patients had diagnostic electrocardiographic changes, and 2 of them did not show significant elevations of temperature, white-cell count or erythrocyte sedimentation rate; the third, J.C., had a course and electrocardiographic changes compatible with acute pericarditis.

The individual and mean of daily determinations of malic dehydrogenase activity on 7 patients with acute myocardial infarction are shown in Figure 1*B*. In each case the activity was elevated two to eight times the normal level. Figure 3 demonstrates that serum malic may be considerably higher than serum lactic dehydrogenase activity, whereas the converse is shown in Figure 4.

Serum zinc determinations on 8 patients with acute myocardial infarction (Table 2) were significantly lower than zinc concentrations of normal subjects. The range for those patients was 41 to 81, with a mean of 67 ± 13.8 microgm. per 100 ml. The normal values ranged from 80 to 165, with a mean of 120 and S.D. of ± 19 microgm. per 100 ml.[19]

Figure 5 shows that the sequential probability ratio test indicated that after 8 observations the mean serum zinc concentration of patients with acute myocardial infarction would be lower than 81 microgm. per 100 ml., at a level of confidence of 99 per cent.

Figure 3 presents the results of sequential determinations of the serum zinc concentrations of 1 patient with a proved myocardial infarction. As described previously, the serum malic and lactic dehydrogenase activities are also plotted on this figure. The serum zinc of this patient was within the normal range, 95 microgm. per 100 ml., on the day of infarction; by the second day it had fallen to 70 microgm., where it remained without change until the tenth day after infarction. On the sixteenth day, the serum zinc concentration had risen to normal, 86 microgm. per 100 ml.

DISCUSSION

Both lactic and malic dehydrogenase activity may be measured as the oxidation of their substrates, lactate or malate respectively, or as the reduction of the products of the reaction, pyruvate or oxaloacetate:

1. L – lactate + DPN^+ $\xrightleftharpoons{LDH}$ L – pyruvate + $DPNH + H^+$
2. L – malate + DPN^+ $\xrightleftharpoons{MDH}$ oxaloacetate + $DPNH + H^+$

In either event the appearance or disappearance of the absorption spectrum due to reduced diphosphopyridine nucleotide at 340 millimicrons is measured, and the choice of the particular reaction to be standardized is conditioned by a variety of factors: the equilibrium of the reaction; the competition of other substrates with the "normal" substrate; the inhibition of the enzyme by the product or substrate of the reaction; and the presence and level of substrate in serum.[22]

These considerations entered into the selection of the choice of the lactate to pyruvate reaction for the assay of lactic and of the oxaloacetate to malate reactions for the malic dehydrogenase activities. Both methods have proved themselves reproducible, precise and simple for routine use. The chemicals required are readily and economically available and easily stored. The determination of lactic dehydrogenase activity is somewhat more convenient than that of malic, since it can be performed immediately and without a twenty-minute period of delay, necessary to allow the interfering reaction pyruvate lactate to go to completion before oxaloacetate can be added. This fact accounts for the lesser number of determinations of malic dehydrogenase activity reported.

The instrumental and technical facilities required are simple and available in most laboratories. The determination requires 0.2 ml. of serum, and the activity of the enzyme does not change appreciably on storage of serum at 4°C. for ten days, thus further simplifying the operational problems of the determination. Avoidance of hemolysis presents the only important precaution that must be observed in the

TABLE 1. *Serum Lactic Dehydrogenase Activity of Patients with the Diagnosis of Suspected Acute Myocardial Infarction.*

CASE NO.	PATIENT	AGE	SEX	DAY OF OBSERVATION*	SEDIMENTATION RATE	WHITE-CELL COUNT	LACTIC DEHYDROGENASE	ELECTROCARDIOGRAM	FINAL DIAGNOSIS AT DISCHARGE
		yr.			*mm./hr.*	*x10³*	*units/ml.*		
1	H.B.	62	M	3	5	8.0	30	(?) Early anteroseptal infarction	Coronary insufficiency
				5			75		
2	R.W.	60	M	1	4	9.0		Anteroseptal infarction (?) early	Coronary insufficiency
				2	8	8.95		Anteroseptal infarction of uncertain age	
				3			40		
3	A.C.	45	M	1	32	13.5	85	(?) Old posterior infarction	Hiatus hernia
				5	14	7.2			
4	S.S.	83	F	2			55	Minimum RST-segment depression in Leads V_1-V_6	Angina pectoris
				4	26	9.1			
5	P.J.J.	56	M	2	28	8.35	45	Hypertrophy of left ventricle	Epidemic pleurodynia†
				4	27	9.0			
6	W.W.	47	M	2	5	10.75	40	Left-bundle-branch block	Probable viral pneumonitis
				5	4	7.2			
7	J.G.	72	M	2		9.0	95	Myocardial ischemia	Congestive heart failure
				4	20	6.95			
				7	28	10.1			
				10			75		
8	J.M.	89	M	7	17	6.4		Posterior myocardial infarction of uncertain age	Congestive heart failure
				11			115		
9	D.M.	71	F	2		11.4		Old anteroseptal infarction	Angina pectoris & congestive heart failure
				3	18	9.7	130		
				6			95		
				8			90		
10	M.D.	66	F	1	24	6.65			Coronary-artery disease with old myocardial infarction
				2	22	6.65	115	Myocardial ischemia	
				5			85		
				8			100		
11	B.E.	47	M	1		14.0		Normal electrocardiogram	(?) Acute myocardial infarction or possible coronary thrombosis without infarction
				2	9	10.9		Normal electrocardiogram	
				4	7	9.8	85	Normal electrocardiogram	
				9			110	Inverted T waves in Leads V_2 & V_3 on day 12	
				14	2	10.1	60		
12	M.F.	61	F	1	18	9.5		Inverted T waves in Leads V_2-V_5	(?) Acute myocardial infarction
				2			85	Inverted T waves in Leads V_2-V_5	
				3	10	10.2	70	Inverted T waves in Leads V_2-V_5	
				4			65	Inverted T waves in Leads V_2-V_5	
				5			100	Reversion of T waves to normal	
				6	12	8.15	105		
13	J.C.	50	M	1	5	13.0		RST-segment elevation in Leads V_2-V_5; ? pericarditis; ? early anteroseptal infarction.	Coronary-artery disease & acute myocardial infarction
				2	31	14.5	65		
				4			120		
				6	26	7.1	110	Subsidence of RST-segment changes; myocardial ischemia.	
				9			70		
				14		12.4	45		
				16	27	6.7	80		

*Day 1 represents day of suspected infarction.
†Maximum temperature of 100°F.; axillary friction rub on left.

obtaining and handling of the sample, since erythrocytes exhibit considerable lactic dehydrogenase activity. Samples should be clotted, centrifuged, and the serum should be separated and stored in the cold a few hours after the blood is drawn.

Serum activity in healthy adults ranged from 25 to 100, with a mean of 59 ± 19 LDH units. Exercise did not change the normal serum activity appreciably. Activity in patients hospitalized for diseases other than acute myocardial infarction ranged from

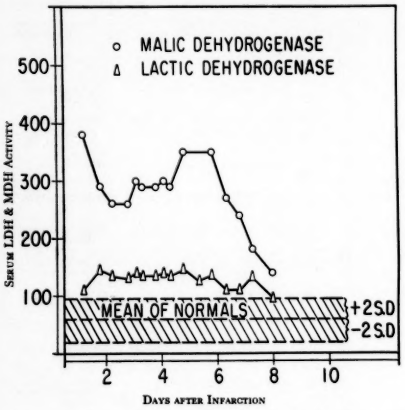

FIGURE 4. *Serial Serum Lactic and Malic Dehydrogenase Activities in a Patient with Myocardial Infarction.*
Enzyme units are defined in Figure 1 and in the text. (Note that the absolute malic dehydrogenase activities are higher than the lactic dehydrogenase activities here — a reversal of the enzyme findings in Figure 3.)

40 to 115, with a mean of 69 ± 20 LDH units. Three groups of patients — those with renal necrosis, hepatitis or cirrhosis of the liver — are not included in this classification. Both groups demonstrated markedly elevated serum activities. Activity was also elevated in renal infarction and subacute glomerulonephritis, as well as in 1 patient with acute tubular necrosis due to mercury ingestion. It has not been found elevated in simple uremia due to chronic renal disease. Activity was normal in several patients with cerebral thrombosis, in 1 patient with acute pulmonary infarction and in another with simple gangrene of the toes. In 2 patients with cholelithiasis and cholecystitis, activity was also normal.

Lactic dehydrogenase activity was uniformly elevated in the serums of patients with acute myocardial infarction rising most commonly on the first day to a peak on the second or third day and falling to normal within seven to eleven days. These data appear to be in substantial agreement with preliminary data published while this work was in progress.[23] Enzymatic activity has not been increased in patients with chest pain accompanied by the electrocardiographic pattern of myocardial ischemia or left-ventricle strain.

Among 16 patients admitted to the hospital with suspected myocardial infarction, 3 manifested conclusive evidence of infarction while in the hospital, and in all 3 the serum lactic dehydrogenase activity rose promptly to abnormal levels. The symptoms and signs of 7 patients were shown to be due to conditions other than myocardial infarction, and the serum activity was uniformly normal (Cases 1-7, Table 1). On the basis of clinical data, 3 of the remaining 6 patients were considered to have sustained acute myocardial infarction, even though diagnostic electrocardiographic findings did not develop (Cases 11-13, Table 1). The remaining 3 were thought to have had myocardial ischemia, severe angina pectoris or congestive heart failure (Cases 8-9, Table 1). Activities were normal or only very slightly elevated, leading to the conclusion that myocardial infarction did not occur in all 6 patients.

TABLE 2. *Serum Zinc Concentrations of 8 Patients with Acute Myocardial Infarction.*

PATIENT	AGE	SEX	SERUM ZINC*
	yr.		*microgm./100 ml.*
A.D.	62	M	70
J.C.	72	M	41
F.B.	67	M	55
J.H.	59	M	60
J.M.	54	M	78
E.R.	69	F	79
A.S.	71	M	81
M.B.	78	F	70

*Mean = 67 ± 13.8 microgm./100 ml.
Normal mean = 120 ± 19 microgm./100 ml.

The patterns of malic dehydrogenase activities are in general similar to those of lactic dehydrogenase both in the mean and standard deviation of the normal group. In each case in which malic dehydrogenase activity was measured, it increased in acute myocardial infarction and the results of serial determinations paralleled the lactic dehydrogenase curves. The time course and degree of increased activity were almost the same as that observed for serum oxaloacetate transaminase activity.[17,18]

Serum zinc concentrations of patients recovering from acute myocardial infarction are significantly decreased. The fall in serum zinc occurs within a day of the onset of infarction and is maintained for as long as two weeks. It then returns to the normal range. The serum concentration of zinc is decreased in several other pathologic states, notably cirrhosis of the liver[19] and pernicious anemia.[24] It is of note that the serum lactic and malic dehydrogenase activities are also increased in patients with cirrhosis of the liver.

The use of the sequential probability ratio test has previously been shown to be a potent tool for clinical investigation.[19] This technic of sequential analysis permits the collection of a statistically significant number of observations in an efficient manner and also indicates the point at which the experiment may be terminated. Wald[25] has shown that this test settles the validity of a hypothesis at any desired level of significance. In the present study the hypothesis that the mean serum zinc concentration of patients with acute myocardial infarctions is below 82 microgm. per 100 ml. can be accepted at the 99 per cent level of significance after eight observations.

It is important to emphasize that an increase in enzyme *activity* does not correspond necessarily to an increase in enzyme *concentration*. The rate of a reaction catalyzed by an enzyme can be increased by the appearance of activating substances or by the removal of inhibitors. The highly purified group of zinc dehydrogenases, of which lactic dehydrogenase is a member, are markedly activated by the removal of contaminating metal ions that are not essential to the enzyme. It has been demonstrated, in fact, that the very metal that is part of the lactic dehydrogenase molecule and is indispensible to its activity will greatly inhibit its activity when added to the purified enzyme as an ion.[26] Subsequent removal of

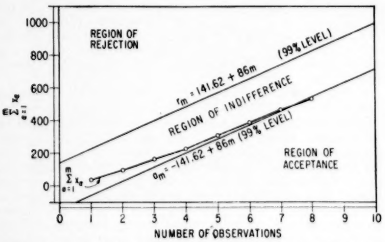

FIGURE 5. *Sequential Probability Ratio Test Applied to the Serum Zinc Concentrations in 8 Patients with Myocardial Infarction.*

$$\sum_{a=1}^{m} x_a$$

The sequential curve $\alpha = 1$ ***is plotted and crosses the acceptance line after eight observations. This indicates that the serum zinc level in 99 out of 100 patients with this disease will be lower than 82 microgm. per 100 ml. of serum, as described in the text.***

such ions will markedly activate the enzyme. It might be suggested that the apparent contradiction of a falling zinc concentration concomitant with the rise in activity of a zinc-containing enzyme partially explains this very phenomenon. The removal of zinc extraneous to lactic dehydrogenase brings about an activation of this enzyme.

The data indicate that the determination of serum lactic dehydrogenase activity can play an important part in the diagnosis of myocardial necrosis. Although not absolutely specific for this condition, pathologic states in which the enzyme levels have been shown to be elevated also do not enter into the differential diagnosis of acute myocardial infarction. It is realized that further studies on a variety of clinical states, especially pulmonary infarction and pericarditis, are needed before the exact specificity of the dehydrogenation reactions can be determined. The negative data obtained on patients suffering from gall-bladder disease should assist materially in eliminating this condition from the differential diagnosis.

Because the Beckman spectrophotometer is not readily available to all clinical laboratories in an era in which enzymology has increasing clinical significance, it is desirable to have available smaller inexpensive instruments, adaptable for routine colorimetry. Such an instrument has recently been designed in this laboratory.[27] The lactic and malic dehydrogenase activities can readily be determined with this instrument, which can be adapted to any enzyme system measured on the basis of the oxidation or reduction of diphosphopyridine nucleotide and will easily allow serum enzyme studies to be performed as a routine procedure.

SUMMARY AND CONCLUSIONS

Serum lactic and malic dehydrogenase are stable in all human serum studied and readily assayed.

Activities for both were elevated two to ten times above those normally observed in all cases of clinically proved myocardial infarction.

Serum zinc levels are lowered significantly after acute myocardial infarction.

Serum lactic dehydrogenase activity is not elevated in angina pectoris, severe coronary insufficiency and myocardial ischemia.

Although serum lactic dehydrogenase rises in other pathologic states, such as renal necrosis and parenchymal liver disease, it is relatively precise and useful to employ this test for the diagnosis of acute myocardial infarction.

We are indebted to Dr. George W. Thorn for his advice and encouragement, to A. F. Bartholomay for his guidance in the use of sequential analysis and to Miss Lois Hersum for her technical assistance.

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IDIOPATHIC ULCERATIVE ESOPHAGITIS*

Report of a Case

HART ACHENBACH, M.D.,† JOSEPH P. LYNCH, M.D.,‡ AND RICHARD W. DWIGHT, M.D.§

BOSTON

THIS is a report of an unusual case of ulcerative disease of the esophagus that began in the lower third, progressed over a period of months and finally involved the entire length of the esophagus. There was loss of much of the mucosa and destruction of the muscular coats in several places leading to stenosis and multiple perforations, which caused abscesses in the mediastinum and right lung. Complicating processes included: perianal abscesses and fistulas; erythema nodosum; migratory arthritis; pyoderma gangraenosum; splenomegaly; and hepatic dysfunction. These complications, the patient's youth and his rapid deterioration suggested ulcerative colitis, but ulcers were found only in the esophagus. Esophagectomy was performed as a life-saving procedure and was followed by remarkable clearing of these associated conditions. A review of the available literature[1-8] has not revealed a similar case.

CASE REPORT

J.A.MC. (B.V.A.H. 10480), a 25-year-old man, was first seen in August, 1953, because of tenderness and discharge in the anal area of 4 days' duration. For more than 1 year, he had had recurrent episodes of tenderness in that region relieved by spontaneous drainage. The first of these occurred during service in Korea. He was a well developed young man, 193 cm. (6 feet, 4 inches) tall, weighing 89.8 kg. (198 pounds). There were no physical defects except 1 abscess and 3 fistulous openings in the perianal region. Laboratory findings were normal except for a hemoglobin of 11.5 gm. per 100 ml. Two subsequent admissions in October and November of the same year were for similar complaints. Biopsy of a fistulous tract on each of these occasions showed granulation tissue with nonspecific chronic inflammation.

The 4th admission, in December, 1953, was for increasing perianal drainage. After his previous hospitalization, he had frequent attacks of pain and swelling of both knees, lasting 3 to 5 days. Examination showed multiple fistulae-in-ano. In addition both knees were noted to be swollen and red, with marked effusion on the left. There were multiple ill defined red plaques on the skin of both legs and thighs, without pain or pruritus (this condition was diagnosed as erythema nodosum by a dermatologist). During the following weeks several of these broke down, forming necrotic undermining ulcers. Cultures of these grew beta-hemolytic streptococcus and *Staphylococcus aureus*. The fluid from the left knee joint was sterile. Sigmoidoscopy and barium studies of the entire gastrointestinal tract were completely negative. Tuberculin and Frei-antigen skin tests were negative, as were biopsies of the muscle and bone marrow. Biopsies of the skin ulcers showed nonspecific acute and chronic ulceration. Blood preparations for L. E. cells were negative. The patient was seen by various consultants, who predicted that ulcerative colitis, regional enteritis or rheumatoid arthritis, or all 3, would develop. After 2 months in the hospital and treatment with antibiotics and compresses to the ulcers, he was discharged only slightly improved.

The 5th admission in April, 1954, again was for perianal drainage. Again, erythema nodosum of the lower extremities and arthritis of both knees were found. He had lost 4.5 kg. (10 pounds) in weight, and the hemoglobin was 9.5 gm. per 100 ml. On April 15 a fistulotomy was done. After this procedure he complained of difficulty in swallowing solid foods. A barium-swallow examination was interpreted as being negative, but a review of the films showed thickening of the longitudinal folds of the esophagus (Fig. 1*A*).

The arthritis became migratory, involving the ankles, wrists, toes and fingers in fairly rapid succession. The hair turned gray. Skin lesions continued to appear on the legs, and now also on both forearms. Cortisone therapy produced

*From the Surgical Service, Veterans Administration Hospital.

†Assistant in surgery, Fifth Surgical Service (Harvard), Boston City Hospital; formerly, chief resident, Surgical Service, Veterans Administration Hospital.

‡Assistant clinical professor of surgery (thoracic), Tufts University School of Medicine; chief, Thoracic Surgery Service, St. Elizabeth's Hospital; thoracic surgeon, Veterans Administration Hospital.

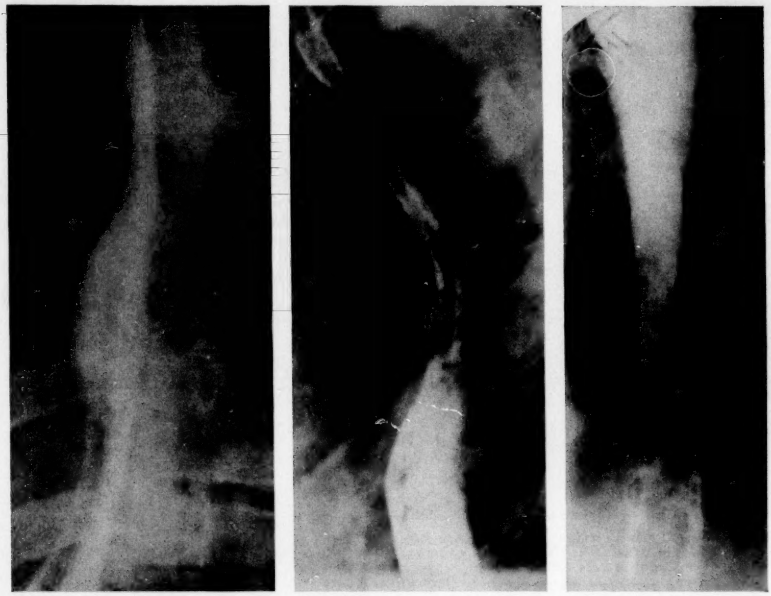
§Associate professor of clinical surgery, Boston University School of Medicine; lecturer in surgery, Tufts University School of Medicine; assistant chief, Surgical Service, Veterans Administration Hospital.

euphoria but no objective change in either the joint or skin lesions.

Dysphagia gradually became worse, and a barium-swallow examination 8 weeks after the first disclosed pseudopolyps with partial loss of the mucosa in the lower esophagus. The gastric mucosa was normal (Fig. 2). By September, the ulcerations involved half the esophagus, and almost complete obstruction had occurred (Fig. 3*B*). Esophagoscopy showed hyperemia of the mucosa, with a stricture at 38 cm. from the upper teeth. Although dilatations produced marked improvement of swallowing ability, they were discontinued because a barium-swallow study indicated undermining of the mucosa. It also disclosed progression of the disease to a level above the arch of the aorta (Fig. 4*B*). The dysphagia again became worse until complete obstruction supervened. During these months the patient had several episodes of jaundice. Liver-function studies during this admission showed alkaline phosphatase levels up to 21.4 Bodansky units, and bilirubin levels of 4.4 mg. per 100 ml., most of it giving a direct reaction. The cephalin flocculation, bromsulfalein retention and thymol turbidity were all normal. In November a feeding gastrostomy was done. This afforded an opportunity for abdominal exploration. The only findings were some enlarged lymph nodes in the porta hepatis and a spleen twice the normal size. A biopsy of the liver showed "a normal liver with slight periportal fatty metamorphosis." The lymph nodes were normal.

Early in December signs of infection were noted in the upper lobe of the right lung. This progressed to abscess formation. A study with Dionosil outlined a fistulous tract between the upper part of the esophagus and the abscess. Bronchoscopy gave no evidence of communication with the tracheobronchial tree. Esophagoscopy disclosed ulcerations with undermined edges and a stricture at 25 cm. Biopsy of the ulcers showed nonspecific acute and chronic inflammation. Treatment with postural drainage and antibiotics produced almost complete healing of the abscess cavities. On January 6, 1955, the esophagus was removed from the cardia to a point just above the clavicle, incisions through the right side of the chest and the left side of the neck being used. After esophagectomy, 1 attempt was made to establish continuity by bringing a loop of jejunum into the chest. This failed because the vascular pedicle was too short. The patient's convalescence from each procedure was slow because of poor wound healing and because diarrhea developed when gastrostomy feedings were increased. However, by January, 1956, from a low point of 54.4 kg. (120 pounds), he was regaining his weight.

Examination of the esophagus (Fig. 4*A*) showed multiple fistulous openings, which had communicated with the mediastinum and with the upper lobe of the right lung. The mucosa of the lower half was almost completely absent, and that of the upper portion undermined and largely detached, forming an elongated, sleevelike structure lying loose in the



A B C

FIGURE 1. *Films from Barium-Swallow Examinations.*

A=*a film taken a week after the onset of symptoms. Note the widening of longitudinal folds in the distal 8 cm. This was constant.*

B=*film of the middle portion on the esophagus, taken on May 3, 1954, showing edematous, widened folds and granular mucosa.*

C=*film taken on June 17. Note the barium-filled fissures, 4-5 mm. in depth, on the edge and the destroyed mucosal pattern. The fissure extended upward for 18 cm.*

lumen except for a few points of attachment. At 1 point the remaining mucosa suggested a pseudopolyp. The entire wall was markedly thickened and stiff.

Microscopical examination showed nonspecific chronic inflammation with fibrosis replacing much of the muscular layer at the level of the stricture. In the lining of a large paraesophageal sinus tract there were foreign-body giant cells. There was no evidence of tuberculosis, scleroderma, amebiasis, cancer or other specific diseases.

FIGURE 2. *Enlarged Film Taken on June 30, Showing Polypoid, Rounded Intraluminal Defects up to 9 Mm. across and Loss of Mucosa between. The gastric folds are normal.*

DISCUSSION

The vast majority of cases of esophagitis are of the peptic type due to reflux of gastric juices, probably associated with an incompetent cardiac sphincter. Ulcers in these cases are usually superficial, but deep chronic peptic ulcers may occur in the distal esophagus, and eventually result in stricture. Pain is a prominent symptom of this type of ulcer. Tuberculosis, syphilis, amebiasis and mycotic infections are rare causes of esophageal ulcers. The diagnosis in these cases can usually be established by the specific pathological picture.

This patient had diffuse, nonspecific ulcerating disease of the esophagus of which painless dysphagia was the first symptom. The first demonstrable abnormality was thickening of the longitudinal folds of the esophagus seen on x-ray examination. The mucosa became fissured and then ulcerated, with undermining and pseudopolyp formation. The esophagus lost its motility and became stenotic and obstructed. Multiple perforations caused abscesses in the upper lobe of the right lung and in the mediastinum.

The removal of the esophagus was a turning point, and gradual improvement became evident. The perianal fistulas were completely resistant to therapy until esophagectomy, after which drainage from the anal area subsided spontaneously. The arthritis, erythema nodosum and gangrenous skin ulcers, which were becoming more severe and widespread despite cortisone and antibiotic therapy, were also resolved. All these have been described as complications of ulcerative colitis, and when they occur this diagnosis must be considered even in the absence of

A B

FIGURE 3. *Films from Barium-Swallow Examinations Three Months* (A) *and Four Months* (B) *after the Onset, Showing an Irregular Lumen with Fissuring and Widened, Almost Vermiform, Longitudinal Ridges* (A) *(Disease Has Extended Almost 31 Cm. up from the Cardia). In the later film* (B) *there is definite, constant narrowing of the lower half of the esophagus, with irregular polypoid filling defects. Note the proximal dilatation above the stricture. No barium entered the stomach.*

colonic symptoms. The etiology of such complications is not understood. They may represent toxicity from a gastrointestinal tract that is more permeable than normal or a decrease in resistance to infection in a chronically ill patient, or they may be an integral part of a disease complex. In this patient the diagnosis of ulcerative colitis was often entertained, but it was never substantiated by barium-enema study or sigmoidoscopy. In any event, esophagec-

tomy apparently cured the associated arthritis, skin lesions and perianal trouble, as colectomy does in ulcerative colitis. This appears to be a disease similar to ulcerative colitis, but occurring in the esophagus.

A B

FIGURE 4. *Esophagus after Removal* (A), *with a Comparable X-Ray Film* (B).

A long pseudopolyp caused the filling defect in the barium-swallow study. The mucosa below this is entirely absent except for a thin regenerating layer in a few places.

SUMMARY

A case of idiopathic ulcerative disease primary in and confined to the esophagus is described.

Associated with this primary disease were migratory arthritis, erythema nodosum, dermatitis gangraenosa and multiple perianal abscesses and fistulas.

In many ways this condition is reminiscent of ulcerative colitis.

To the best of our knowledge no similar cases are recorded in the literature.

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EYEBALL BRUITS*

JONAS H. COHEN, M.D.,† AND STANLEY MILLER, M.D.‡

BALTIMORE

SELDOM do physicians, including ophthalmologists, employ auscultation over the face and head areas as an adjunct to clinical observation. More routine use of the stethoscope over the eyeball itself will demonstrate the presence of bruits that are overlooked because hitherto they have been associated with few specific concomitant findings. More frequent auscultation may reveal the presence of a bruit as a sign in some relatively common pathologic entities. Within a period of two years, 7 cases of eyeball bruit were discovered by us on the medical service of a 370-bed general hospital. A review of the literature and communication with ophthalmologists reveal that little comment is available concerning bruits so localized to the eyeballs that they cannot be heard over the bones of the orbit or skull. This is illustrated in 6 of the 7 cases reported below.

*From the Department of Medicine, Sinai Hospital.

†Adjunct attending physician, Sinai Hospital.

‡Adjunct attending physician and attending hematologist, Sinai Hospital.

CASE REPORTS

CASE 1. R. B., a 60-year-old seamstress, was admitted to the Sinai Hospital with the complaint of frontal headache, which began 3 months before hospitalization. After this, pain in the scalp, hyperesthesia, alopecia, tinnitus and diminished hearing, all on the left side of the head, developed. Anorexia, failure of memory and weakness of both legs were also present.

On examination at the hospital, a systolic bruit was heard over the left eyeball. The bruit disappeared on compression of the left common carotid artery. It persisted despite changes in the patient's position. She complained of a noise in her head. Because of age and language difficulty one could not determine the relation, if any, to the complaint of tinnitus. The blood pressure was 175/65. Generalized arteriosclerosis was marked. Funduscopic examination showed only mild arteriosclerotic retinopathy. There was extreme tenderness over the left aspect of the scalp, ptosis of both upper lids, more marked on the right, and irregularity of both pupils, only the right one of which reacted to light and accommodation. Neurologic examination, lumbar puncture, blood chemical findings and a serologic test for syphilis were not remarkable. Routine x-ray studies of the skull were within normal limits, except for increased vascular markings on the left side. An arteriogram revealed a definite constriction and angulation of a

loop of the left carotid siphon (Fig. 1). The bruit disappeared for 3 days after arteriography and then returned, but was less intense. The patient was discharged unimproved and was readmitted to the hospital 3 weeks later with mental confusion, motor aphasia, right-sided facial weakness and right-sided hemiparesis. The bruit this time was only faintly audible. The patient improved somewhat, and the bruit then completely disappeared.

About 1 year later she died of arteriosclerotic gangrene of a lower extremity. At no time was there recurrence of the bruit.

FIGURE 1. *Arteriogram, Showing Constriction and Angulation of a Loop of the Left Internal Carotid Siphon.*

CASE 2. E. K., a 60-year-old housewife, was admitted to the hospital with the complaint of a right-sided headache of 4 weeks' duration. She had been hypertensive for 5 years, and had bronchial asthma and chronic gall-bladder disease. A year before admission she was treated with shock therapy for a psychotic episode characterized by mania, hallucinations and loss of memory.

Four weeks before admission the right-sided headache was first noted, followed a week later by the sudden onset of thick speech and the sound of "rushing in the head." Ten days before admission a systolic bruit was discovered above the right orbit, but was found to be loudest over the right eyeball. It was audible also behind the right ear and over the right mandibular area. Compression of the right carotid artery caused complete disappearance of the bruit. The bruit persisted despite any change in position. Marked systolic murmurs were heard over both carotid areas. Over the precordium there was a systolic blow, heard loudest at the aortic region. The peripheral vessels were sclerotic and tortuous. The blood pressure ranged from 170-200, systolic, to 80-100, diastolic. Funduscopic examination revealed marked arteriolar narrowing, with moderate arteriovenous nicking. Babinski, Oppenheim and Gordon reflexes were positive. X-ray study of the skull was negative.

The patient's condition remained unchanged until 4 days after admission, when an arteriogram was obtained by the injection of the right common carotid artery. This was interpreted as showing variability in the diameter of the lumen in the S-shaped portion of the internal carotid artery (Fig. 2). In the middle portion of the siphon there were 2 relatively narrowed constrictions. Immediately after this procedure, the patient experienced a severe asthmatic reaction as well as incoherent speech and left-sided weakness, which varied in intensity and extent during the next 12 days. In this period her blood pressure dropped to normal levels, and a mild secondary anemia was noted. On the 17th day after admission she appeared to be at her lowest ebb, as evidenced by aphasia, disorientation, incontinence of urine and stool and full-blown left-sided hemiplegia. From this point on she showed moderate improvement and was discharged to her home during the following week. Six months later there was still some aphasia and left-sided hemiparesis. The bruit was not as loud as when originally discovered, but could still be heard 1 year later.

CASE 3. H. K., a 37-year-old house painter, was admitted to the hospital with the chief complaint of inability to move the left side of his body. He had been in good health until the day of admission, when, on his way to work, his left leg became numb and weak and began to drag. Approximately 15 minutes later the left arm became paralyzed, and then the fingers. There was no unconsciousness, paresthesias, convulsions, headache or vertigo.

On physical examination a well defined systolic bruit was present only over the right eyeball and was not heard over the bones of the orbit or skull. Compression of the right carotid artery caused disappearance of the bruit. The blood pressure was 168/80. Funduscopic examination was entirely negative. The deep reflexes were hyperactive, more so on the left than on the right. Positive Hoffman and Babinski signs were present on the left. There was complete paralysis of the left side of the body, not including the face. Spasticity of the left arm and leg was present. There were no sensory changes. A serologic test for syphilis and lumbar puncture were negative.

The patient had a mild headache, and the extremities on the left became flaccid. Diminished abdominal reflexes on the left also developed. X-ray films of the chest and skull were within normal limits. The bruit over the right eyeball gradually became fainter and 12 days later could not be heard. An encephalogram was unsatisfactory because of poor filling. An arteriogram showed a block of the right internal carotid artery as it entered the cavernous sinus (Fig. 3). Gradually, function returned to the affected side, and with the aid of physiotherapy, the patient improved rapidly. A mild postoperative bronchopneumonia developed, but was quickly controlled with penicillin. He was discharged to continue physiotherapy at home.

FIGURE 2. *Arteriogram, Showing Variability of the Lumen in the S-Shaped Portion of the Internal Carotid Artery.*

CASE 4. E. K., a 15-year-old schoolboy, was admitted to the hospital with the chief complaint of weakness of the right arm and leg and headaches since 1946. In July, 1941, projectile vomiting, severe generalized headache with delirium and "stiffness all over" suddenly developed. Eight lumbar punctures were done, which were all bloody (according to his mother). The patient remained in another hospital for 3 weeks and apparently recovered satisfactorily. At home 3 days later, he suffered an epileptiform convulsion and was unconscious for more than 15 minutes. There were no further symptoms until 1946, when he suddenly noticed weakness of the right arm and leg. This was associated with a severe generalized headache. These symptoms disappeared after 3 days, when a similar episode again occurred, this time with transient aphasia. The right lower extremity appeared to become progressively weaker. He walked with a decided limp. Attacks of weakness and numbness in the right arm also occurred. He stated that he had had a constant tremor of the hands since 1938. During the week before admission, he noticed that his words became mixed up when he tried to talk rapidly.

On physical examination, a loud systolic bruit was heard over both eyeballs, but more marked on the left side. Compression of the left common carotid artery caused the left eyeball bruit to disappear, but obliteration of the right had no effect on the bruit over the right eyeball. The blood pressure was 100/64. Funduscopic examination was negative. There was slight but definite atrophy of the right calf and shortening of the right extremity. Neurologic examination revealed hyperactivity of the deep reflexes on the right side, with a positive Babinski sign. There was no sensory disturbance, but there was a definite muscular weakness of the right lower extremity. A serologic test for syphilis was negative. Lumbar puncture revealed normal dynamics and cell count and a negative Pandy test. Spinal fluid and blood chemical findings were also within normal limits. An electroencephalogram showed a normal record. X-ray examination of the skull was negative. An arteriogram disclosed a large vascular matting in the posterior parietal region (Fig. 4). It was diagnosed as a hemangioma.

The patient's course in the hospital remained unchanged and he exhibited no other unusual symptoms. On examination 7 years later, the eyeball bruits were unchanged.

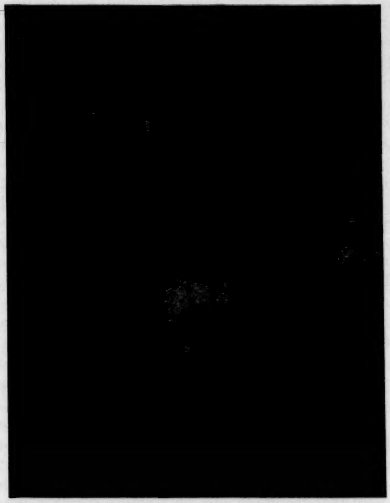

FIGURE 3. *Arteriogram, Showing a Block in the Right Internal Carotid Artery As It Enters the Cavernous Sinus.*

CASE 5. P. L., a 63-year-old woman, was admitted to the hospital with the complaint of intermittent cramplike pains in the left flank and left upper quadrant, with nausea of 2 months' duration. She also complained of bloating, belching and constipation associated with these symptoms. There was no frequency or dysuria.

She had been admitted to the hospital 10 years previously with similar complaints, and at that time a horseshoe kidney with a small calcification in the upper pole of the right kidney was found. The symptoms abated, and she was discharged improved. At that time her blood pressure ranged between 190/98 and 150/90. From that time until the present, she had suffered from numerous headaches, palpitations and anginal attacks. The headaches were located over the right parietal region and were associated with a "roaring and buzzing" in the right ear. She had also noticed fatigue and weakness for the past 8 years. The past history and family history were otherwise noncontributory.

Physical examination revealed an obese, well developed female in no apparent distress. A harsh systolic bruit was heard only over the right eyeball. Compression of the right carotid artery obliterated the murmur. The bruit varied moderately in intensity from day to day, and at times was almost inaudible. The blood pressure was 210/92. The heart was slightly enlarged, the border of density extending to the left. A soft systolic murmur was heard over the apex and base. The liver edge was palpable 2 fingerbreadths below the right costal margin. The lower poles of the kidneys were palpable and tender, more so on the left. There was generalized arteriosclerosis.

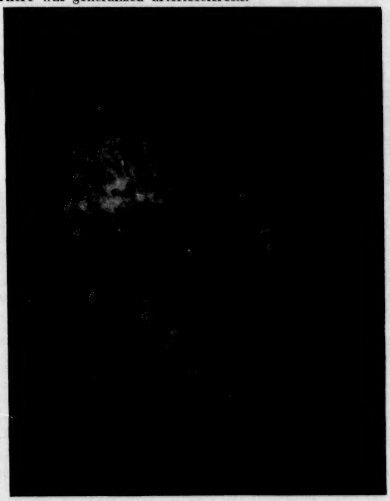

FIGURE 4. *Arteriogram, Showing a Large Vascular Matting over the Posterior Parietal Region.*

Urinalysis revealed an occasional white blood cell in the sediment, and the culture grew *Staphylococcus aureus*. The remaining laboratory data were within normal limits. X-ray examination of the skull was negative. A plain film of the abdomen and an intravenous pyelogram again demonstrated a horseshoe kidney with a small calcification. An electrocardiogram was interpreted as showing chronic coronary insufficiency.

The patient was asymptomatic except for headaches during her stay in the hospital. The bruit was still audible at the time of discharge 7 days later. No arteriogram was attempted, on the advice of her physician.

CASE 6. I. R., a 48-year-old woman, was admitted to the gynecologic ward service at the hospital with a history of vaginal bleeding of 1 month's duration and "spots in front of her eyes" for 3 weeks before admission. On examination a bruit was heard over both eyes that was systolic in time. The bruit was not audible elsewhere over the head.

Examination of the heart revealed an accentuated pulmonic 2d sound, preceded by a rough Grade 3 systolic murmur in the pulmonic area, and a softer systolic murmur in the aortic region. At the apex a Grade 2 systolic bruit was heard, as well as a rough presystolic murmur. The blood pressure was 140/66. These findings were thought to be hemic murmurs because of the severe microcytic hypochromic anemia that was present as a result of the excessive bleeding. Funduscopic examination revealed normal disks and vessels, except for some pallor. Further examination disclosed some puffiness of the eyelids and a ++ pitting edema of the ankles.

After transfusions with 3000 ml. of blood and a subtotal hysterectomy for fibromas and adenomyosis of the uterus, the patient made an uneventful recovery. Examination of the blood on admission revealed a red-cell count of 1,820,000, with a hemoglobin of 2.9 gm. per 100 ml. and a hematocrit of 15 per cent; the white-cell and platelet counts were normal. After the patient had received 2500 ml. of blood on the 3d day after admission, the bruit over the eyeballs had disappeared. At this time the hemoglobin was 9.9 gm. per 100 ml., the hematocrit was 34 per cent, and the red-cell count 3,730,000.

CASE 7. J. W., a 35-year-old housewife, was admitted to the hospital with the complaint of generalized weakness of 2 weeks' duration. Exertional dyspnea and fatigability became marked before she consulted her physician. She was told that she was very anemic. Four days before admission she complained of dizziness and was put to bed. It was then noticed that her skin was yellowish. There had been no hematemesis or melena. She stated that as a child she had had several bouts of jaundice and had had an enlarged liver. She also stated that she had had syphilis in 1935. The family history was noncontributory.

On physical examination loud, blowing bruits, systolic in time, were heard over both eyeballs. They were not heard over any other portion of the skull. Soft, blowing systolic murmurs were present at the apex and base of the heart. The blood pressure was 120/50. The liver edge was palpable 3 fingerbreadths below the right costal margin. Funduscopic examination revealed some tortuosity of the arterioles, and there were 2 flame-shaped hemorrhages in the right fundus. The other notable physical finding was an enlarged spleen, which was palpable 5 fingerbreadths below the left costal margin.

The red-cell count was 1,360,000, with a hemoglobin of 5.6 gm. per 100 ml., and the hematocrit was 17 per cent. A leukopenia and thrombocytopenia were present. A serologic test for syphilis was positive, with a titer of 1:64. The red-cell count continued to drop despite repeated transfusions. There was increased fragility of the erythrocytes, and spherocytosis was present. The lowest red-cell count reached was 600,000, with a hematocrit of 7.5 per cent. The diagnosis was congenital spherocytosis.

Three weeks after admission a splenectomy was done. On the next day the red-cell count had reached 2,530,000, with a hematocrit of 27 per cent, without the benefit of transfusions. The bruit over the eyeballs disappeared on this day and did not recur. The red-cell count hovered between 2,500,000 and 3,500,000. The patient has been under constant observation as an outpatient since discharge from the hospital.

DISCUSSION

Eyeball bruits, reported in cases of hyperthyroidism and severe primary and secondary anemias, have been observed bilaterally,* as in Cases 6 and 7. Unilateral bruit has been noted in conditions secondary to trauma such as arteriovenous aneurysms or in neoplastic conditions such as outer-ridge meningiomas. Bruits can be produced by the mechanism of pressure exerted by a mass on the blood vessel and also in association with intermittent exophthalmos. Walsh[1] mentions the occurrence of bruit on one side, with eye signs on the other based upon an abnormal communication between cavernous sinuses or upon an ophthalmic-vein thrombosis. Osler[2] wrote of head murmurs in children and cited Jurasz's theory that the carotid canal may cause a relative stenosis, owing to the lag in expansion of the bony passage as compared to the expansion of the artery itself. One of the commonest causes of intracranial bruits is aneurysmal angioma. Two other more frequent causes, in our experience (4 cases), are thrombosis and arteriosclerosis of the internal carotid artery. In all our cases, it must be emphasized, the bruits were either localized at or heard most loudly over one eyeball, except in the 2 cases of severe anemia. In Hamburger's[3] observations concerning various types of head murmurs congenital vascular anomalies and atheromatous and dilated carotid arteries are mentioned as causes of head bruits. Dow[4] examined 16 internal carotid arteries at autopsy and remarked that in the neck the carotid canal was subject only to a few atheromas but that the part of it that lay in the cavernous sinus was affected extensively.

First mention of cephalic bruit in the medical literature was made by Fisher,[5] of Boston, who in 1833 described a "cephalic-bellows" sound and discussed its possible importance in cerebral diseases. Sir Victor Horsely is said to have made auscultation of the head a usual practice during his examination of the nervous system. Osler, too, emphasized the importance of cephalic auscultation. Hamburger,[3] in 1931, and Mackby,[6] in 1942, summarized the literature pertaining to head murmurs. Mackby advocated auscultation over both temporal fossae, the posterior mastoid prominence and the middle of the forehead.

It is our purpose to emphasize the frequency with which the head murmur may be localized at the eyeball in the same case in which it may be inaudible over the orbital bones or other nearby structures. Therefore, auscultation of the head should routinely include the application of the stethoscope to the eye itself, especially in cases of neurologic and circulatory diseases in which no bruit is audible over the cranium. It is emphasized that the patient should be examined in sitting and supine positions, as well as while lying on each side.[7]

Head bruits of several different types have been described. In some cases the patient himself is not aware of it. It is conceivable, on the other hand, that an exploratory operation may serve to accentuate a sound that the mechanics of a closed chamber previously served to dampen, though this would be difficult to explain on physical principles. Cushing and Bailey[8] maintain that a soft, blowing sound may occasionally be heard over skulls of infants; it is otherwise scarcely heard over the cranium even in cases of true intracranial aneurysms. We noted that the quality of the bruits heard was similar in all 7 of our cases, although the intensity varied not only from patient to patient but also from time to time in the same patient. All the bruits were synchronous with the heart beat and were systolic in time. The sound itself was a soft, blowing murmur. Often, the stethoscope had to be placed with just the proper amount of pressure, and the patient was requested to hold his breath while the examiner held the other eye closed or the patient opened the other eye. Bruits

*Recently a systolic bruit was heard over the left eyeball of a patient with hyperthyroidism. The left lobe of the thyroid gland was enlarged, and the bruit was heard only over this lobe.

could be made to disappear by pressure on the ipsilateral common carotid artery, except in cases of anemia.

The vibration-composing murmurs are said to travel in all directions with an intensity proportional to the intensity at the source, and proportional to the ability of the tissues to transmit sound. Bone is said to be suited to the transmission of sound because of its rigid and continuous structure.[9] This is a point, however, that is in disagreement with our findings, since we detected bruits over the soft tissues of the eyeball that were not heard over the surrounding bony structures. Perhaps the explanation is that the source of the bruits was closer to the bell of the stethoscope over the eyeball than to even the nearest bone.

The transiency and variability in intensity of the murmur noted in all our cases posed an interesting question of the mechanism involved. In 3 cases of narrowing or occlusion of the internal carotid artery as demonstrated by arteriograms[10] (Fig. 1, 2 and 3), the bruit disappeared, only to recur three days later in Case 1 and finally fading out four weeks later. In Case 3 the bruit disappeared in twelve days and never recurred. The initial disappearance in both cases occurred immediately after arteriography. In the other case (Case 2) of internal-carotid-artery narrowing and possible thrombosis, the bruit diminished notably in intensity, though without complete disappearance.

Arteriosclerosis of the internal carotid artery, causing angulation of the vessel and narrowing and finally culminating in complete occlusion or thrombosis, may be the explanation for the presence of the unilaterality, transiency and localization of the bruit. That there is angulation and constriction of the vessel along the carotid siphon in the cavernous portion of its course seems adequately demonstrated by the arteriograms (Fig. 1 and 2). Saphir,[11] in discussing tumorlike plaques in the cavernous portion of the occluded carotid arteries, calls attention to the development of the collateral circulation, which can take over the functions of the occluded vessels, unless there is heart failure or the development of extra burdens on the circulation. In Case 1, in which the bruit disappeared, the patient failed steadily, dying six months later of various complications of generalized arteriosclerotic deterioration. In Case 3, in which the bruit also disappeared, the course was one of slow improvement, with some return of function of the paralyzed portion of the body. It seems reasonable to postulate that in Case 1 there was, in all probability, a very poor collateral circulation, whereas in Case 2 there was good collateral circulation. The age disparity may well have been a major factor in the final outcome in these 2 cases. In disappearing, the bruits gradually became less intense. There was no sudden cessation. This supports the concept that a process of complete thrombosis or recanalization is a comparatively slow one. Moniz[12] states that the slowness of formation of the thrombus and the less advanced age of the patient may contribute to the progressive dilatation of the communicating vessels. The rapidity of the onset of the thrombus, the advanced age of the patient and the arteriosclerosis of the vessels, on the contrary, will make the prognosis unfavorable. In Case 4 (of Moniz) the onset of the internal-carotid-artery thrombosis was preceded by an aphasia lasting only a few minutes. This was followed by a bruit heard in the left eye that lasted only one day. Sorgo[13] concludes that almost all thromboses of the internal carotid artery are caused by arteriosclerosis, other vascular disease or trauma. Galdston et al.[14] point out that hemiplegia due to internal-carotid-artery thrombosis is not as uncommon as it was formerly thought to be. In their opinion, the cause of this type of thrombosis is not always clear. Sclerosis of the aorta, pressure from an aortic aneurysm, syphilitic and nonsyphilitic arteritis and embolism are the conditions that they found most often associated with carotid-artery thrombosis.

The presence or absence of bruit as a diagnostic sign of true aneurysm of the carotid artery is a point that has been debated in the literature. Beadles[15] stated that cephalic bruits are most commonly associated with true intracranial aneurysms of any of the large arteries at the base of the brain. He found only 2 cases of bruit associated with true aneurysm — 1 of the vertebral artery and 1 of the cavernous portion of the internal carotid artery. Walsh and King[16] reported only 1 case in 33 in which a bruit was associated with a saccular aneurysm; the bruit was heard best over the left eye and faintly over the right. Cushing and Bailey[8] stated that bruits, when present, usually point to the diagnosis of aneurysmal angioma rather than true aneurysms. It has been pointed out by at least one observer[15] that the presence of a bruit may be significant in a case in which mental disorders associated with auditory hallucinations (hissing, waterfalls and buzzing) and mental or neurologic disorders associated with observable organic disease must be differentiated.

Summary

Seven cases of eyeball bruit occurring in a 370-bed general hospital during a two-year period are presented. Two cases were proved, and 1 was suspected to be due to arteriosclerotic narrowing of the carotid siphon. One case was proved to be caused by internal-carotid-artery thrombosis in the cavernous portion. One was due to hemangioma, and 2 cases were proved to be caused by profound anemia.

Except for the 2 anemia cases and the case of angioma, the other 4 cases were examples of unilateral bruit.

In 6 of the 7 cases, the bruit was localized to the eyeball itself.

Attention is called to the relative frequency of eyeball bruits, especially those caused by occlusion

and narrowing of the cavernous portion of the internal carotid artery.

More frequent application of the stethoscope to the eyeball, as well as the head and orbit, is urged as a valuable adjunct in the diagnosis of cerebrovascular diseases.

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ENDOCARDIAL FIBROELASTOSIS IN INFANTS ASSOCIATED WITH THROMBOSIS AND CALCIFICATION OF ARTERIES AND MYOCARDIAL INFARCTS*

Wilbur A. Thomas, M.D.,† Kyu Taik Lee, M.D.,‡ Malcolm H. McGavran, M.D.,§ and Erwin R. Rabin, M.D.¶

ST. LOUIS, MISSOURI

CALCIFIC arterial disease of infants with myocardial infarcts is uncommon, but at least 50 cases have been reported in the medical literature.[1,2] The etiology has remained a complete mystery. It has been suggested that the arterial changes result from a basic defect in calcium metabolism.[1,2] However, no such defect has been demonstrated, and the general distribution of the lesions is not that of diseases known to result from abnormalities of calcium metabolism. Another possibility is that the disease results from a defect in the formation of elastic tissue and that the calcium deposition is a secondary feature.[1-3] The nature of the defect (if it exists) is unknown.

In a recent survey at Washington University of autopsied patients who died with acute myocardial infarcts, we discovered 2 infants who had died with myocardial infarcts resulting from advanced disease of the coronary arteries with calcification. We decided to review the material from these patients in an effort to obtain some clue to the etiology and pathogenesis of the disease. The material from these patients has also been compared with that from other patients and from animals with myocardial infarcts. The object of this report is to present the results of our study.

*From the Department of Pathology, Washington University School of Medicine.

Supported in part by grant H-1820 from the National Heart Institute, National Institutes of Health, United States Public Health Service, Bethesda, Maryland.

†Assistant professor of pathology, Washington University School of Medicine; assistant pathologist, Barnes Hospital.

‡Professor of medicine, Taegu Medical School, Taegu, Korea; formerly, Life Insurance Medical Research Fellow in Pathology, Washington University School of Medicine.

§Resident in pathology, Washington University School of Medicine; assistant in pathology, Barnes Hospital.

¶Intern in pathology, Grace-New Haven Community Hospital.

Material and Methods

The autopsy protocols and microscopical sections from 2 infants with calcific arterial disease and myocardial infarcts were reviewed. The gross specimens were no longer available since the autopsies were performed many years ago. All microscopical sections were stained according to standard technics with hematoxylin and eosin, and selected sections were stained with aldehyde-fuchsin-van-Gieson-hematoxylin, Masson's trichrome, phosphotungstic acid-hematoxylin, periodic acid-Schiff, Heidenhain's connective-tissue stain, Verhoeff's elastic-tissue stain and von Kossa's calcium stain.

Similar material was reviewed from other patients and from a group of laboratory animals as follows: 24 infants who had died with uncomplicated endocardial fibroelastosis without valvular involvement; 2 infants each of whom had a left coronary artery arising from the pulmonary artery and who had associated myocardial infarcts; 1 infant who died with endocardial fibroelastosis, complicated by mural thrombosis and myocardial infarcts but without calcified arterial lesions; and 5 rabbits with myocardial infarcts resulting from embolization with blood clots.

Results

Infants with Calcific Arterial Disease and Myocardial Infarction

One infant (R.J.) was two months, and the other (C.S.) three months old at the time of death. Both were males and were considered to be in good health before the terminal illness. R.J., in whom dyspnea

developed two weeks before death, was admitted to the hospital, where he died with signs and symptoms of circulatory failure. C.S. manifested respiratory difficulty and died in the hospital twelve hours after the onset of symptoms.

Complete autopsies were performed on each. The only significant abnormalities observed grossly were of the heart. The heart of each infant was greatly hypertrophied (R.J.'s was approximately three times the normal size, and C.S.'s was twice the normal size), and the hypertrophy was principally of the left ventricle. Multiple partial occlusions were noted in the coronary arteries of both infants. The mural endocardium in the left ventricle of C.S. was said to be "mottled," and that of R.J. was considered to be "normal." "Fibrin tags" (perhaps mural thrombi) were found attached to the left ventricular endocardium of C.S. Gray streaks were noted in the left

FIGURE 1. *Organized Thrombus Containing Calcium in a Coronary Artery of C. S. (Verhoeff's Elastic-Tissue Stain, X50).*

ventricular myocardium of R.J., and yellow foci were noted in the left and right ventricular myocardium of C.S. The valves and atria were normal.

Microscopically, similar changes were noted in the coronary arteries of both infants. The changes were focal, many sections of coronary arteries appearing normal. Clearly recognizable organized thrombi containing calcium were seen in many of the abnormal foci (Fig. 1). Marked intimal thickening in other foci in the coronary arteries may have been the result of organized thrombi or simply a proliferative reaction of the intima to injury (Fig. 2). In many vessels the elastic and muscular coats were partially or completely destroyed and replaced by fibrous tissue containing calcium. In some the elastic and muscular coats were better preserved, with degeneration and calcification limited to the area immediately beneath the internal elastic membrane. However, in all abnormal vessels the changes were so advanced in the intima and media

FIGURE 2. *Coronary Artery of C. S., Showing Calcification and Markedly Thickened Intima Possibly Resulting from Organization of a Thrombus (Hematoxylin and Eosin Stain, X70).*

that it was impossible to determine precisely where the process began. Some lymphocytes and monocytes were scattered throughout the walls of the abnormal vessels, but they did not form the prominent part of the picture.

In both infants foci of necrosis were noted in the myocardium, especially in the subendocardial region. In some foci muscle fibers had disappeared entirely (even though the duration of symptoms in R.J. was only a few hours). In other foci coagulated muscle fibers were still present. Histiocytes, lymphocytes and neutrophils were present in both hearts. Deposits of calcium were present in some of the necrotic areas of the myocardium of C.S. (Fig. 3).

The left ventricular endocardium of each infant was markedly thickened by fibrous and elastic tissue (Fig. 4). In R.J. the thickening was uniform in the available sections, but in C.S. the thickness of the

endocardium varied. Some areas in C.S. were greatly thickened, and others were only slightly thickened. The fibrous tissue in the thickened endocardium was more dense and less cellular than the younger-appearing fibrous tissue in the myocardium. In some areas the thickened endocardium was adjacent to foci of necrotic myocardium, but in others the myocardium beneath was intact. No clearly recognizable mural thrombi were seen in the available microscopical sections.

FIGURE 3. *Myocardial Infarct Containing Calcium from C. S. (von Kossa's Calcium Stain, X50).*

Examination of sections from various other parts of the bodies of both infants revealed many normal-appearing arteries, but some in various sites showed changes indistinguishable from those in the coronary arteries. The involved sites included the pancreas, adrenal glands, skeletal muscle and pelvic connective tissue. A small scar, which could have represented a healed infarct, was found in one of R.J.'s kidneys. No other areas of infarction or calcification and no other significant gross or microscopical abnormalities were noted.

Comparative Groups

Two infants (aged four months and five months) with the left coronary artery arising from the pulmonary artery. Extensive areas of muscle necrosis with fibrous-tissue replacement were noted in the hearts of both these infants. In both, foci of calcification were present in the necrotic muscle. Both had advanced fibroelastic thickening of the endocardium of the left ventricle. In both patients connective tissue in the endocardium and in the destroyed myocardium appeared to be of about the same age. No lesions were noted in the coronary arteries.

Twenty-four infants with endocardial fibroelastosis without valvular involvement or other defects. All these infants had fibroelastic thickening of the endocardium of the left ventricle indistinguishable from that in C.S. and R.J. None had mural thrombi or evidence of systemic or pulmonary embolization. None had coronary-artery changes. All had greatly hypertrophied hearts (weighing twice to four times the expected weight).

One infant with endocardial fibroelastosis complicated by myocardial infarction without calcific arterial lesions. This infant, two and a half years of age, had typical endocardial fibroelastosis with advanced hypertrophy of the heart. Associated with the endocardial fibroelastosis were mural thrombi, coronary-artery lesions consistent with organized thromboemboli and healed myocardial and renal infarcts. Calcification was not present in the arteries or infarcts.

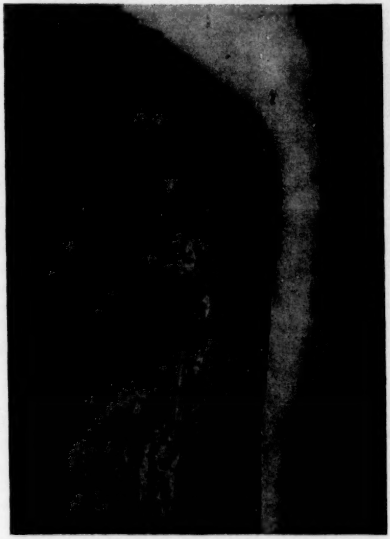

FIGURE 4. *Markedly Thickened Endocardium of the Left Ventricle of C. S. Extending into the Sinusoids (Masson Stain, X70).*

Five rabbits with myocardial infarcts resulting from embolization with blood clots. Fragments of blood clots (obtained from other rabbits) were injected into the left ventricle of 5 rabbits through an 18-gauge needle. All these rabbits, which were killed three to twenty days after the injections, had one or more

healing myocardial infarcts. Deposits of calcium were found in most of these infarcts. None developed fibroelastic thickening of the endocardium. The thromboemboli injected into these rabbits were small and did not occlude large vessels such as those that were occluded in R.J. and C.S. Calcification was not found in the small vessels that were occluded.

Discussion

The association of endocardial fibroelastosis with calcific arterial disease has not been reported previously, and raises a number of questions regarding the relation between these processes. Since both diseases are uncommon it seems unlikely that the relation between them is simply fortuitous. (The possibility that this combination occurred by chance in 2 other patients is less than 1:1,000,000 autopsies.) If the relation between the two processes is not fortuitous, several possibilities must be considered:

The possibility that the myocardial infarcts result in the development of endocardial fibroelastosis. Our first impression was that this possibility was the most likely because myocardial infarcts in adults are often associated with fibroelastic thickening of the overlying endocardium.[4] However, the histologic appearance of the fibrous tissue in the endocardium suggests that it is older than that in the infarcted myocardium. The collagen in the infarcted myocardium is rather loose and cellular whereas that in the endocardium is more dense and less cellular. Moreover, the extreme cardiac hypertrophy (found in both C.S. and R.J.) is typical of endocardial fibroelastosis but unusual with uncomplicated myocardial infarction (at least in adults).

Thus, it seems likely that the endocardial fibroelastosis antedated the myocardial infarction, and hence could not have been caused by it.

The possibility that the calcific arterial disease alone (without the aid of myocardial infarcts) caused the endocardial fibroelastosis. This possibility cannot be excluded. The lesion in the arteries and the endocardial thickening both appear to be of long duration and cannot be dated with certainty. However, the appearance of the endocardial changes at least suggests that they are older than the changes in the coronary arteries.

The possibility that endocardial fibroelastosis results in the development of calcific arterial disease with myocardial infarction. It was not immediately apparent how endocardial fibroelastosis could cause arterial disease and myocardial infarcts. On reflection, however, a mechanism occurred to us whereby endocardial fibroelastosis could result in arterial disease and myocardial infarcts — these could have resulted from emboli originating from mural thrombi attached to the endocardium.

In a previous study[4] we demonstrated that mural endocardial thrombosis and embolization were common in patients older than two years of age with endocardial fibroelastosis. Fifteen of 18 such patients (aged two to seventy-one) had some evidence of thrombosis or thromboembolism. Furthermore, 1 of the patients (aged two and a half) used for comparison in the current study had endocardial fibroelastosis with mural thrombi, thromboembolism and myocardial and renal infarcts. It would not be surprising to find thromboembolism in occasional younger patients. Mural thrombi in the heart were not demonstrated on the microscopical sections from either R.J. or C.S. (aged two and three months respectively). However, "fibrin tags" attached to the left ventricular endocardium were described grossly in 1 of them. The presence of completely organized mural thrombi could have been obscured by the already thickened endocardium. The myocardial infarcts in both R.J. and C.S. contained calcium, which is not usually found in adults with infarcts of similar duration. However, we found calcium in myocardial infarcts of 2 infants (aged four and five months) whose left coronary arteries arose from the pulmonary arteries. Furthermore, myocardial infarcts produced in the rabbits by thromboembolism (used in this study in part to test this specific point and in part to show that myocardial infarcts could be produced readily by embolization from the left ventricle) contain large quantities of calcium. Thus, it seems in infants and rabbits that calcification in myocardial infarcts can occur readily. Calcification of thrombi can also occur in young infants, as demonstrated in a previous study.[5]

The random distribution of the arterial lesions (in C.S. and R.J.), with normal-appearing vessel walls elsewhere, is consistent with thromboembolism. Most of the arterial lesions are associated with clearly recognizable organized thrombi, and all arterial lesions are associated with some type of intimal lesion that could represent an organized thrombus. Degeneration of the arterial wall beneath an organized thrombus has been noted in other patients.[6] Thus, it seems possible that the endocardial fibroelastosis could result in the development of calcific arterial disease with myocardial infarcts.

The possibility that some unknown agent caused both the endocardial fibroelastosis and the calcific arterial disease with myocardial infarcts. Since the etiology of both diseases is unknown, this possibility must be considered. We have no clue to what this agent may be. Neither the clinical findings nor the distribution of the lesions suggest a derangement of calcium metabolism.

Summary and Conclusions

A study of the etiology and pathogenesis of calcific arterial disease of infants with myocardial infarcts is presented based on 2 autopsied patients with this dis-

ease, 2 infants with the left coronary artery arising from the pulmonary artery, 24 infants with uncomplicated endocardial fibroelastosis, 1 infant with endocardial fibroelastosis complicated by mural thrombosis and myocardial infarcts without calcific arterial lesions and 5 rabbits with myocardial infarcts resulting from thromboembolism. Both infants with calcific arterial disease and myocardial infarcts were found to have in addition endocardial fibroelastosis (characterized by fibroelastic thickening of the endocardium of the left ventricle and cardiac hypertrophy). This association has not been described in previous reports.

Since both diseases are uncommon, it is unlikely that they are associated only by chance. The relation between the two diseases can be explained in several ways. The most likely possibility seems to be that endocardial fibroelastosis was the underlying process and that the arterial disease and myocardial infarction resulted from thromboembolism. Evidence is presented supporting this hypothesis, and alternative possibilities are discussed.

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MEDICAL PROGRESS

NEUROLOGY

WILLIAM K. JORDAN, M.D.,* AND H. HOUSTON MERRITT, M.D.†

LITTLE ROCK, ARKANSAS, AND NEW YORK, NEW YORK

AS in other branches of medical science, the volume of the neurologic literature has increased with each succeeding postwar year, thereby making a comprehensive review difficult. A large number of American and foreign journals and monographs have been culled in preparation of this article, and an effort has been made to select for presentation material that we consider of particular interest and usefulness to the readers of this journal. Advances in the fields of neurophysiology, vascular disease of the brain, epilepsy, muscle disorders, headache and Wilson's disease, as well as in several miscellaneous areas, are described.

Anatomy and Physiology

Experimental work of the past few years has led to increased knowledge of the physiology of the limbic system (defined below) and of the anatomic structures and physiologic processes concerned in consciousness and recollection of previous experiences. Many of these findings are of aid to the clinician in understanding the anatomy and physiology of the various phenomena of the convulsive disorders, of disturbances in levels of consciousness and perhaps of behavioral disturbances. Also, light has been shed on the modes of interaction between two of the great "integrator" systems of the body — the nervous and endocrine systems.

*Professor of neurology, University of Arkansas Medical Center.

†Professor of neurology, Columbia University College of Physicians and Surgeons.

Limbic System

The limbic system — to which the term "visceral" brain has also been applied — is usually defined as encompassing the limbic lobe of Broca and its subcortical cell stations. The term "limbic lobe" was originally applied by Broca to the cortical areas surrounding the hilus of the hemisphere and includes the cingulate gyrus, subcallosal and retrosplenial gyri and the pyriform area, hippocampal gyrus and the infolded hippocampus. The subcortical cell stations of this system are the amygdala, septal nuclei, hypothalamic centers, anterior thalamic nuclei, portions of the basal ganglions and perhaps the epithalamus. The island of Reil, the anterior pole of the temporal lobe and the medial and posterior orbital gyri are closely related to this system, although not a part of it by definition. This system has a relatively constant gross and microscopical structure throughout the mammalian phylogenetic scale, and has been contrasted with neocortical areas by Fulton[1] in the following words:

> A clear cut distinction can now be made between the two great systems of the forebrain: (1) the phylogenetically ancient limbic complex which is concerned with autonomic reactions involved in emotional expression and only secondarily with intellectual function, and (2) the somatic neocortex which presides primarily over higher intellectual functions. Both systems are to be found in the anatomical frontal lobe.

Much experimental work has been done in elucidating the various functions of this system, but only a few reports can be selected for description here.

Kaada[2] and others[3] have shown that the limbic system and related structures have a profound influence on the regulation of cardiovascular respiratory and alimentary functions, and have suggested that this system may be regarded as the primary autonomic area of the forebrain.

Bates[4] has shown that stimulation of the limbic cortex, in patients undergoing hemispherectomy for infantile hemiplegia, evokes gross movements, first in contralateral and later in ipsilateral limbs. These movements are not discrete, as are those evoked by stimulation of neocortical areas, but massive, and resemble "in some respects the assumption of a posture, or the performance of components of a simple act such as climbing. . . ."

Baldwin et al.[5] found that stimulation of the amygdala in primates results in complex movements of the face and jaws, resembling the facial movements evoked by stimulation of the inferior mesial temporal region in man.

The relations of this system to "emotional" behavior are exemplified by experiments reported by MacLean.[6,7] When the posterior portion of the hippocampal formation is stimulated electrically with sufficient stimulus strength to produce an afterdischarge, the animal assumes attitudes of rapt attention or fearful alerting for the unexpected, and is poorly in contact with his environment. Emotional changes that may be induced during an afterdischarge are most interesting. An animal that before stimulation simply meows when the tail is pinched will hiss, spit and strike out if a noxious stimulus is applied during the afterdischarge. Prolonged or repeated noxious stimuli may lead to states of wild excitement accompanied by spitting and hissing.

Kaada[2] has observed that the spread of the afterdischarges resulting from strong stimulation of the limbic system, and considered by some to resemble seizure activity, has the tendency to be confined to the limbic system. MacLean[6] has emphasized the fact that there may be a spread of hippocampal discharges within the limbic system without a discernible alteration of neocortical activity. He has pointed out that a seizure activity largely confined to the limbic system may have a bearing on some aspects of epileptic behavior as well as on the postepileptic amnesia of patients with psychomotor epilepsy. He refers to Hughlings Jackson's famous Case Z, a young doctor who during a fit was able to stoop over and pick up a pin and to continue the physical examination of a patient and to write a reasonable diagnosis, all with a subsequent amnesia for what had happened; he was found at autopsy to have a small area of softening in the region of the left uncinate gyrus. MacLean[6] states that it is inconceivable that acts requiring both manual and intellectual skill could be performed in the absence of functioning neocortex. The occurrence of seizure activity in the limbic system without appreciable alteration of cortical activity possibly gives some insight into the mechanism of such epileptic behavior.

MacLean also points out that the sudden explosion of fury elicited by stimulation of the hippocampus resembles the behavior of some patients with psychomotor epilepsy when an effort is made to thwart their actions during a seizure.

Temporal Lobe

Observations made in the course of over twenty years of stimulating the temporal lobe have been summarized and interpreted recently by Penfield.[8] He described the occurrence of psychic responses that could sometimes be elicited by stimulation of the lateral and superior surfaces of the temporal lobe in epileptic patients. He states that when stimulation of the exposed cortex produced such psychic responses in a conscious patient, it seemed that the patient was reliving an earlier experience in the greatest detail. Although he retained awareness of his actual surroundings, there was a re-experiencing of visual, auditory and even somatic sensations. This reliving of previous experiences could only be activated in a temporal cortex that had been somehow conditioned by years of electric discharges from a neighboring epileptogenic focus.

In commenting on the relation between memory, as ordinarily defined, and the type of recall elicited by electric stimulation, Penfield states that there is a great difference between the stimulatory replaying of a strip of record of the stream of consciousness and the voluntary act of recollection. Memory, as ordinarily defined, is something else and includes many generalizations and is often progressively influenced by subsequent experience.

In discussing the location of the ganglionic mechanism concerned in the preservation of the record of the stream of consciousness, he states that the actual recording mechanism may be in the cortical gray matter where the stimulating electrode seems to awaken it or it may be in areas that give no response to direct stimulation, such as the hippocampus and hippocampal gyrus. But if it is in such a zone there must be specialized connections between that zone and the areas of temporal cortex, stimulation of which produces the memory responses. He concludes that, regardless of the way, it is not going beyond the evidence to assume that this area of cortex must play an important part in the formation or preservation of the record of the stream of consciousness.

Consciousness

Particular attention has been focused recently on the important roles of the ascending reticular system[9] and the diffuse thalamocortical projection system[10] in maintenance of the state of alertness or awareness of environment to which the clinician usually refers by the term "consciousness."

Thus, Foltz and Schmidt[11] have demonstrated that in experimental concussion in the monkey the sensory-evoked responses in the reticular formation were selectively and uniformly absent, the responses in the more direct pathways to the thalamus, the lemnisci, being unchanged. They conclude, "Since unconsciousness is the single major criterion for cerebral concussion, since loss of sensory activation of the reticular formation results in unconsciousness, and since these two conditions were experimentally produced simultaneously, it is postulated that the unconsciousness produced by cerebral concussion is at least in part the result of the sudden loss of sensory activation, or 'driving' of the brain stem reticular formation."

Bailey[12] has recently examined, in an illuminating critical essay, the relation of consciousness to neural structures. He does not minimize the importance of brain-stem structures in this regard:

> Now there is no doubt that our consciousness is altered by many changes in our environment, both internal and external, by lesions of the sense organs and of the nerves which lead from them to the central nervous system, by lesions of the nerves which lead to the effector organs of our behavior and by variations in the nervous impulses coming back to the central nervous system from them (so-called feedback). But these effects on consciousness, although they must be remembered in any attempt to think clearly about the matter, are not what neurologists have in mind when they talk of localization of consciousness. They mean to ask where the smallest lesion in the brain will cause the most profound defect of consciousness. The answer must be — in the bulb. But such lesions are rarely compatible with life so that the area is enlarged to include other portions of the brain stem, notably the pontine tegmentum, midbrain and posterior diencephalon.

However, he cautions against neglect of other neural structures in relation to the problem of consciousness. He describes a patient in whom a disturbance in level of consciousness, clinically resembling that produced by lesions of the brain stem, resulted from anoxic degeneration of the entire neocortex, the brain stem being intact. He gives a reminder of the importance of the cerebral cortex in consciousness in the following forceful manner:

> The kaleidoscopic play which we call the mind goes on primarily in the cerebral cortex (Bailey). That it needs to be heated, alerted, made vigilant like the tubes of a television set, by the reticular formation or other afferent stimulation (Bremer), before it will transmit is quite probable but the consciousness of a human being without a cortex must lead as dim and tenuous an existence as that of the shades in Hades.

Neuroendocrine Relations

The observations of Harris,[13] Hume[14] and others[15] have elucidated the manner in which the nervous system influences the activity of the anterior pituitary body, specifically in relation to control of secretion of ACTH. The stimulation of ACTH secretion seems to depend upon the following sequence of events: activation of one or more of several hypothalamic centers; and passage of nervous impulses to the median eminence of the tuber cinereum, followed by liberation of a chemotransmitter into the hypophyseal portal system, with passage of the chemotransmitter agent to the cells of the anterior pituitary body, resulting in increase in output of ACTH. The evidence in favor of this sequence of events has been summarized by Munson and Briggs[15] as follows:

> Lesions of specific hypothalamic centers, particularly in the median eminence, lead to a decrease in secretion of ACTH in response to various stimuli. Secondly, the stimulation of various hypothalamic nuclei, or the median eminence, results in increased ACTH secretion. Thirdly, pituitary-stalk section, with precautions to prevent revascularization from the hypophyseal portal system, results in adrenal atrophy. And, fourthly, transplantation of the pituitary body to sites isolated from the hypophyseal portal vessels results in adrenal atrophy, whereas grafts placed immediately under the median eminence and revascularized from the hypophyseal portal system maintain normal adrenal weight.

Vascular Disorders

Angiography

Demonstrations by cerebral angiography of displacement of elements of the cerebral arterial system, of tumor staining and of vascular anomalies have proved of value in the diagnosis of space-occupying lesions. Until recently, interest has been centered mainly on the arterial phase. Lately, a number of investigators have emphasized the value of the venous phase of angiography, particularly in lesions of the deep cerebral veins.[16] Lin et al.[17] have constructed an orientation chart for the location of the foramen of Monro through visualization of the "venous angle" of the brain in the cerebral phlebogram, based on the principles employed in constructing charts for the position of the pineal body. The "venous angle" of the brain is the term applied by Richter[16] to the point at which the striothalamic vein turns mesially and slightly inferiorly, hugging the posterior superior border of the foramen of Monro to form the origin of the internal cerebral vein. The anterior convexity of this turn of the "venous angle" signifies radiographically the posterior border of the foramen of Monro. In a study of 26 cases of proved space-occupying lesions[17] the orientation of the "venous angle" was found to indicate that the foramen of Monro can be displaced by sizable space-occupying lesions. Lin et al.[17] point out that although their orientation chart provides a useful basis for studying the position of the foramen of Monro with experience, inspection of the phlebogram and evaluation of the relation of the internal cerebral veins to its tributaries and landmarks in the skull, as well as the configuration of the internal cerebral vein itself, may be of greater diagnostic value than any absolute

measurement made from the roentgenograms. Study of the deep cerebral veins, it is believed, may make possible better diagnosis of deep-seated supratentorial and, perhaps, of infratentorial lesions, both now, in general, considered better localized by air studies.

Olsson[18] and Hauge[19] have reported on use of the catheterization of the radial artery as a technic for vertebral angiography. The catheter is usually inserted through an incision in the radial artery and traced fluoroscopically back to the vertebral artery, after which injection of contrast medium is carried out. Gould, Peyton and French[20] have described the retrograde filling of the vertebral and sometimes the ipsilateral internal carotid circulation in children and adults by retrograde injection in the brachial artery. They believe that this method is of value in children but do not recommend it for adults. Sjögren,[21] in a review of 250 cases of percutaneous angiography, has concluded that the percutaneous technic is less complex than the radial-artery-catheterization technic, that both succeed in about the same percentage of cases and that the choice of site is not limited in the percutaneous method. In discussing the indications for vertebral angiography, Petit-Dutaillis et al.[22] state that percutaneous vertebral angiography is particularly valuable in patients with subarachnoid hemorrhage if bilateral carotid angiography gives normal findings. They point out that it is rarely possible to inject the tumor vessels of posterior-fossa neoplasms, but that occasionally vascular displacements may be of value, particularly those of the basilar artery, in lateral views, and of its bifurcation or of the posterior cerebral arteries in anteroposterior views. Thus far the procedure has not been of use in tumors of the cerebellar hemispheres, but it may be useful in suspected tumors of the cerebellar pontine angle, and in suspected tumors of the mid-line basal structures. Sjögren[21] states that the exact localization of expanding posterior-fossa tumors with vertebral angiography is not as precise as that with air studies. He also points out that the localization of space-occupying masses in the posterior fossa by vertebral angiography is made difficult by the superposition of vessels in lateral views and the covering of the cerebellar vessels by the posterior cerebral arteries in anteroposterior views. There are frequent variations in anatomic arrangement of the arteries. Perhaps most significant is the greatly varying length of the basilar artery. There are also variations in the posterior inferior cerebellar arteries. Olsson[18] believes vertebral angiography to be valuable in the search for aneurysms and for supratentorial tumors in the posterior part of the brain, especially central basal tumors such as gliomas.

Several studies of the complications of cerebral angiography have appeared.[23,24] Kaplan and Walker[23] have discussed this problem, reviewing information on 500 consecutive angiograms in 484 patients at Johns Hopkins Hospital. There was a mortality of 0.8 per cent and a complication rate of 4.6 per cent in their series. Diodrast was the contrast medium used in all cases. The frequency of complications was not related to sex or race. Complications are rarely found in patients with brain tumors, but are more often seen in the presence of vascular disease. Complications are about twice as frequent in patients over fifty than in those under this age. Hemiplegia or hemisensory disturbance occurred in 10 patients, clearing in one or two days in all but 1. Three patients had convulsions, 2 had visual disturbances, and 2 had hematomas in the neck that produced discomfort. Mental confusion did not occur in any of their patients. They believe that some of the complications of angiography are due to toxicity of the dye, but others are related to the technic of arterial puncture and the selection of patients. Prophylactic stellate or cervical block was not valuable in the experience of these authors, nor has the administration of papaverine before dye injection been useful. Once a complication has occurred, immediate procaine injection into the cervical sympathetic ganglions is worth while and at times has produced dramatic improvement. Papaverine intravenously and inhalation of carbon dioxide offer the greatest promise of increasing intracranial circulation, but amyl nitrite and nicotinic acid are of little value. These authors emphasize the fact that treatment of complications must be immediate if it is to be effective. They believe it is safer to wait for nine or ten days after rupture of an aneurysm before angiography is done.

Perese et al.[24] attribute the causes of complications in angiography to clot or thrombus formation, spasm of surface vessels and alterations of the blood-brain barrier, with direct toxic action of the dye and blood constituents on nerve cells. They stress the need for a contrast material less toxic than Diodrast.

Most authors emphasize the value of use of small amounts of injectable material, use of low concentrations of the various Diodrast dyes and avoiding use of these agents in angiography in patients who have cerebral arteriosclerosis. A number of new agents for cerebral contrast angiography have been reported, including Urokon and Hypaque. Seaman and Schwartz[25] report that Urokon is satisfactory but that it too causes complications. It is not possible from the data in the literature to evaluate Hypaque, but it appears promising.

Aneurysms

The clinical localization of intracranial aneurysms and vascular anomalies is discussed by Walker[26] in an article based on analysis of 285 patients with aneurysms or vascular anomalies seen at Johns Hopkins Hospital. He concludes that, although pathognomonic syndromes do not exist, symptoms associated with aneurysms of the internal carotid artery either above or below the anterior clinoid processes

are often sufficiently characteristic to suggest a diagnosis. The clinical picture of the infraclinoid aneurysm without rupture is characterized by third-nerve palsy, with evidence of slight involvement of the upper or middle divisions of the trigeminal; occasionally, exophthalmos may be present. Rupture of this aneurysm usually occurs into the cavernous sinus and is not associated with subarachnoid bleeding. When rupture occurs a noise in the head audible to patient and physician may be the first manifestation, and may be present weeks before the development of exophthalmos, which is a cardinal symptom of the carotid-cavernous-sinus fistula, and is usually unilateral. In 10 per cent of the cases, it is bilateral and may occur in the eye opposite the fistula. There may be pulsation of the eye associated with a thrill on palpation of the orbit (in 90 per cent of cases). Extraocular palsy with impairment of vision is a frequent occurrence, and the trigeminal nerve may be involved. Aneurysms of the anterior cerebral or anterior communicating arteries often produce visual disturbances and, with rupture into the subarachnoid space, coma. Aneurysms of the middle cerebral artery are commonly associated with hemiparesis, and also rupture into the subarachnoid space. Dilatation of the basilar arteries may cause cranial-nerve irritation and brain-stem involvement. Hemorrhage occurs from vascular anomalies or angioma in 20 per cent of such cases. The nature of the lesion may be suspected from a long history of previous epileptic phenomena. A valuable table has been constructed by Walker indicating the cardinal points involved in differentiation of these lesions (Table 1).

In a thoughtful review of the problem of management of patients with subarachnoid bleeding, Magladery[27] has considered the hospital course of 235 unselected patients with subarachnoid hemorrhage. Of these, 37 were subjected to surgical measures. He points out that although the clinical material available for this study does not lend itself to rigorous statistical analysis, it does not support the view that present available surgical means of intervention offer any improvement over the current conservative approach. Regarding conservative therapy he emphasizes the importance of maximal rest during the acute stage, achievement of adequate aeration and alertness to disturbances in electrolyte balances. Some clinicians believe that spinal taps, repeated as frequently as indicated by changes in the vital signs, with maintenance of the intracranial pressure below 200 mm., are valuable. Rowe et al.,[28] in reviewing the literature from 1944 to 1955, point out that the average mortality was 21 per cent in direct attacks on intracranial aneurysms. The mortality after ligation of the carotid artery in the neck was only 8 per cent. They believe that the problem of the relative merits of treatment of aneurysms by ligation of the carotid artery in the neck or by direct intracranial attack remains unsettled. They conclude that doubtless both procedures will have a place. They

TABLE 1. *Incidence of Signs and Symptoms in the Variously Located Aneurysms and Vascular Anomalies.*‡

TYPE OF LESION	BEFORE RUPTURE			CHANCE OF RUPTURE	AFTER RUPTURE IN SUBARACHNOID SPACE									
					INVOLVEMENT OF CRANIAL NERVES							COMA	HEMIPARESIS	CONVULSIONS
	ASYMPTOMATIC	HEADACHE	PARESIS OF 3D CRANIAL NERVE		2d	3d	4th	5th	6th	7th	8th			
Supratentorial vascular anomalies	+*	+	0	+	0	0	0	0	0	0	0	++	++	+
Aneurysm of internal carotid artery:														
Infraclinoid	0	0	++++	+	+	++++	+++	+	+++	0	0	+	0	0
Carotid-artery-cavernous-sinus fistula	0	+	++†	0										
Supraclinoid	++	++	++	+++	+	++	+	0	0	0	0	+	+	+
Aneurysm of anterior cerebral & communicating arteries	++	++	0	+++	+	0	0	0	0	0	0	+++	+	+
Aneurysm of middle cerebral artery	+	+	0	+++	0-	0	0	0	0	0	0	++	++	+
Aneurysm of posterior communicating & cerebral arteries	+	+++	+	+++	0	++	+	+	+	0	0	+	+	+
Aneurysm of vertebral & basilar arteries	++	+	0	+++	0	0	0	0	0	+	+	+++	+	0

*Convulsions common.

†Syndrome of pulsating exophthalmos, bruit & at times ocular palsies.

‡Rating:

0 = 0-5%
+ = 5.1-35%
++ = 35.1-65%
+++ = 65.1-95%
++++ = 95.1-100%.

point out, however, that ligation of the carotid artery in the neck may result in a higher late mortality owing to recurrent hemorrhage, although this point needs further investigation.

Basilar-Artery Insufficiency

The syndrome of intermittent insufficiency of the carotid artery has been known for many years. Recently, attention has been called to a similar syndrome of the basilar system.[29] The latter diagnosis is suggested when a symptom such as hemiparesis occurs on opposite sides of the body in attacks in conjunction with such phenomena as dimness of vision throughout the visual fields, dysarthria, dysphagia and vertigo. The symptoms disappear rapidly, and there are usually no neurologic signs between attacks. The symptoms may become permanent, or death may occur if the vessels become totally occluded.

Anticoagulants

There are at present four fairly well defined situations involving occlusive phenomena of the cerebrovascular system in which anticoagulant therapy seems indicated:

In the first place Millikan et al.[30] report that 5 patients with intermittent insufficiency of the basilar system had their attacks stopped when effective anticoagulant action was obtained; secondly, these authors administered anticoagulants also to 25 patients with basilar thrombosis. The mortality was 12 per cent in the latter series. In the control group of 23 untreated patients the mortality was 43 per cent. Heparin, Tromexan and Dicumarol were the anticoagulants used, and the last was chosen for long-term therapy. The dose of anticoagulant was adjusted to keep the prothrombin time between 30 and 40 seconds (normal, 18 to 20 seconds); thirdly, Wright and McDevitt[31] have reported on the use of anticoagulants in multiple thromboembolic phenomena involving various structures, including the nervous system, secondary to or concomitant with rheumatic endocarditis, atrial fibrillation, mitral stenosis or myocardial infarction. Finally, Millikan et al.[32] have described this form of treatment in intermittent insufficiency of the internal carotid artery. Its use in other types of occlusive phenomena of the cerebral vessels is also being investigated.[31]

(To be continued)

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MEDICAL INTELLIGENCE

OBSERVATIONS ON THE RELIABILITY AND SAFETY OF BLADDER CATHETERIZATION FOR BACTERIOLOGIC STUDY OF THE URINE*

LUCIEN B. GUZE, M.D.,† AND
PAUL B. BEESON, M.D.‡

NEW HAVEN, CONNECTICUT

THE usual method of culturing urine is to obtain a specimen from the bladder by catheterization and inoculate it in liquid mediums. If growth results, urinary-tract infection may be assumed to be present. The reliability of this procedure seems questionable for two reasons. In the first place, although care is taken to cleanse the area around the urethral meatus before insertion of a sterile catheter, there is no practical, harmless way of destroying bacteria that may lie within the urethral channel. These could be transferred into the bladder during passage of the catheter and could then be the origin of bacterial growth in the culture. Secondly, the use of a liquid medium does not yield information on the number of bacteria originally present in the urine, because their rapid multiplication in broth can give nearly maximum growth within a day or two, regardless of the size of the inoculum.

We are reporting some observations bearing on the foregoing points. The studies were made on patients undergoing gynecologic surgery. The catheterizations were done in the operating rooms, with the patients under anesthesia; thus, conditions were optimal for employment of aseptic and antiseptic technic. The routine of preparation included cleansing with green soap, hexachlorophene soap, alcohol and saline solution.

The first aim was to culture the tips of catheters that had been inserted into the urethra. After the usual preparation, a sterile metal or rubber catheter was inserted well into the urethra, then withdrawn for culture. This was done by placing the catheter tip in a small test tube containing 2 ml. of sterile saline solution, which, after being swirled around the catheter, was cultured in an agar pour plate and in thioglycollate broth.

Thirteen such tests were made, and growth was obtained in 6 cases. There was pure growth of *Escherichia coli* in 4, *Esch. coli* and *Staphylococcus aureus* in 1 and *Aerobacter aerogenes* in 1. It appears probable, then, that catheters being passed into the bladder frequently have bacteria on their surfaces, despite stringent precautions.

This finding made it seem likely that bacteria can be introduced into the bladder urine during the procedure of catheterization. To establish this point conclusively it was decided to obtain urine specimens that had not been subject to possible urethral contamination. This was done by aspiration of urine through the bladder wall with a syringe and needle, during laparotomy. These could then be compared with specimens obtained by catheterization shortly afterward. Twelve such observations have been made. In 8, both samples of urine gave no growth.

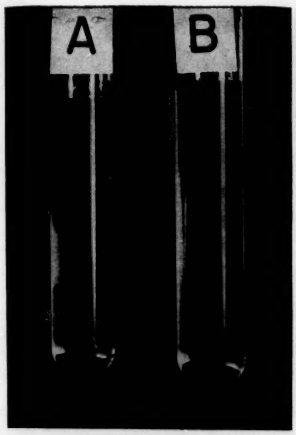

FIGURE 1. *Broth Cultures of Urine Obtained from the Same Patient.*

Tube B was inoculated with urine obtained by needle aspiration of the bladder at laparotomy. Tube A was inoculated with urine obtained a short time afterward by urethral catheterization.

In the remaining 4, however, although urine aspirated from the bladder at laparotomy was sterile, that obtained by catheterization of the same patients a few minutes later showed presence of *Esch. coli* in 3 and *Pseudomonas aeruginosa* in 1. Figure 1 is a photograph of two broth cultures of urine from a single patient; one inoculated with urine aspirated through the bladder wall during operation remained clear, whereas the other, inoculated with urine obtained by catheterization, exhibited luxuriant growth.

*From the Department of Internal Medicine, Yale University School of Medicine.
Aided by a grant-in-aid from the National Institutes of Health.

†National Institutes of Health Research Fellow in Medicine, Yale University School of Medicine; assistant physician, University Service, Grace-New Haven Community Hospital.

‡Professor of medicine, Yale University School of Medicine; physician-in-chief, University Service, Grace-New Haven Community Hospital.

The pour plate made from the positive sample revealed only 3 colonies per milliliter, illustrating how a false impression of heavy "infection" can result from dependence on inoculation of a liquid medium with undiluted urine.

Aside from pointing up the error that may be involved in the usual technic of urine culture these studies support the view that catheterization, no matter how carefully done, carries with it some danger of introducing infection into the bladder cavity. Information on the extent of this risk is surprisingly meager, but there can be no doubt that some chance of infection exists.[1,2] Indeed, in 1 of the patients in the second portion of this study urinary-tract infection subsequently developed. Thirty-six hours after operation she complained of dysuria, and examination revealed pyuria together with large numbers of *Esch. coli.*

It appears, therefore, that methods for bacteriologic examination of urine deserve further consideration, since the mere demonstration of bacterial growth from a sample obtained by catheterization cannot be accepted as proof that the bacteria originally were in the bladder cavity. In view of this, and the hazard of infection from catheterization, it seems desirable to try to employ methods suitable for testing "clean-voided" specimens of urine, by means of quantitative technics, inoculation of solid mediums, study of Gram stains and so forth.[1,3,4] In the work reported here the numbers of contaminating bacteria on the catheter tips and in the urine obtained by catheter were never large — that is, fewer than 100 colonies per milliliter of fluid. In true urinary infection there are usually thousands to millions of bacteria per milliliter of urine.[3]

Summary and Conclusions

Despite employment of meticulous aseptic and antiseptic technic, small numbers of bacteria were sometimes transferred from the urethral canal into the bladder during the passage of a catheter, and these could be recovered in cultures of bladder urine. Thus, catheterization does not provide a completely trustworthy specimen for cultural examination and also is hazardous from the standpoint of initiating infection in the bladder.

We are indebted to Drs. C. L. Buxton, J. McL. Morris, J. H. Monroe and B. S. Waldie, who obtained the specimens in the manner described.

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DOCTORS AFIELD

Frederick Albert Cook (1865-1940)

Nathan P. Couch, M.D.*

BOSTON

DOCTORS Afield, if considered a phylum of the medical kingdom, can be subdivided into two classes: aberrant physicians who still cling to some form of medical practice, and those who do not. Dr. Frederick A. Cook, first in the former group and later in the latter, was an ill starred, infinitely ambitious Brooklyn general practitioner who took up exploring and, as a consequence, became probably the most controversial figure in twentieth-century Arctic history.

Born and raised in the Catskill Mountains, where he developed an early taste for hard winters, he spent his adolescence and collegiate years in New York City. By dint of abundant part-time work, he earned enough money to help support his family and put himself through Columbia college and medical school. He received his M.D. degree in 1889, but the death of his recent bride only a few months later was a fitting omen of the difficult future awaiting him.

Scarcely a year of general practice had passed before Cook accepted a position as surgeon to Robert E. Peary's North Greenland expedition of 1891. Peary quickly learned to respect and appreciate Cook's abilities as a surgeon and rugged explorer, praising his "unruffled patience and coolness in an emergency." In two years, Cook began his own series of Arctic commands on the *Zeta* (1893) and the *Miranda* (1894). During the latter expedition, the twenty-nine-year-old Cook navigated an open boat across 90 miles of malevolent polar sea to obtain help, after the ship foundered on an iceberg. This experience may have literally cooled his enthusiasm, for four years passed before he was off on another polar quest. In 1898 he was surgeon to the *Belgica* expedition when the little vessel became the first to winter in the Antarctic. (This may have been arranged by Cook's somewhat dyspeptic guardian angel, — his private Promethean vulture, — who saw to it that the *Belgica* was unwillingly frozen into the Bellingshausen Sea.) Cook's shipmate, Roald Amundsen, gave him much of the credit for their survival and escape, and he found it hard to believe "that a few years later Cook would be regarded as one of the greatest humbugs the world has ever seen."

In 1900 Cook presented his first book, a narrative of the *Belgica* voyage, *Through the First Antarctic Night*. A year later he was again in the Arctic as Peary's surgeon. Early 1902 found Peary's expedition attempting to reach the North Pole from Cape Hecla

*Assistant in pathology, Peter Bent Brigham Hospital.

(latitude, 83°) at the northernmost tip of Ellesmere Land. Open leads and huge ice hummocks slowed the sledges to a crawl, forcing Peary to turn back at 84°17′. The failure was important in persuading Cook that this so-called "American route" to the Pole was, like Pound's ephemeral lady friend, "much-praised but not-altogether-satisfactory."

In 1903 and 1906, transiently suffering from the Alpinist's itch, he made two attempts to scale Mount McKinley. The first failed because of a wrong approach, but he claimed that the second had succeeded, making him the first man in history to reach the summit. In the later dispute over the North Pole, Cook's antagonists advanced photographic evidence to show that his victory over the Alaskan peak was a fraud. Others confirmed Cook's own story.

Soon after the publication of the explorer's *Harper's* article (1907) on the great economic promise of Antarctic exploration, John R. Bradley offered to finance a North Pole venture, led by Cook. Preparations were rapid and efficient, so that by early 1908 Cook found himself at Annoatok, on the west coast of Greenland, laying final plans for his assault on 90° north, where, the Eskimos imagined, the "Great Nail" rose out of the earth.

When Peary's financial backers learned of Cook's pending attempt, they cried foul, and charged that Cook had unfairly planned the expedition in stealth. They argued that their own champion should have a "fair and final opportunity" to reach the Pole. It was of no importance that the polar venture they were currently financing for Peary was his seventh chance.

Blissfully unaware of the storm he had caused about 2500 miles to the south, Cook left Annoatok for the north in the spring of 1908 with 10 Eskimos, 11 sledges, and 105 dogs. When he arrived at Cape Stallworthy (Svartevoeg) at the northern tip of Axel Heiberg Land, twenty-eight days and 400 miles were behind him; 520 miles still separated him from the North Pole. When his last supporting party turned back after three days' march, Cook was left with 2 Eskimos, 2 sledges carrying 800 pounds apiece, and 26 dogs. At about 85° latitude, he thought he saw a land mass on the horizon west of his trail. According to his claim, he reached the Pole on April 21, made observations for two days and then returned south. Tragedy nearly ended the exploit on countless occasions, for a previously unknown midsummer event, the westward drift of the pack ice, propelled the party through treacherous waters. After their narrow escape from the seething Wellington Channel, they landed on Devon Island, exhausted, without food, and surrounded by a forbidding land. But they obtained enough game and, in an ancient, dugout Eskimo shelter, found enough cover to survive the winter. On April 18, 1909, fourteen months after their departure and twelve days after Peary allegedly reached the Pole, the party of 3, weak and gaunt, walked into the home base. Cook was soon aboard the *Hans Egede*, bound for Copenhagen. In the Shetlands, he wired the Brussels Observatory: "Reached North Pole April 21, 1908 . . ." When Peary sent his two famous telegrams ("I have the Pole, April 6, 1909," and an indignant "Dr. Cook has handed the public a gold brick") the Battle of the Pole had begun.

When Cook and Peary returned from the North, public opinion was clearly divided. The Peary faction was led by the Peary Arctic Club and the National Geographic Society, both organizations numbering several government officials among their influential membership. The Cook supporters were poorly organized, but at one time or another included such Arctic notables as Roald Amundsen, Knud Rasmussen, Otto Sverdrup and Major General A.W. Greeley. The tactics were widely variant, from both logical and ethical standpoints. There were a few careful, objective appraisals, but there were also canny innuendo, *ad hominem* bickering, and even flagrant chicanery. The conclusion of Thomas F. Hall (who wrote a 475 page monograph on the subject) agreed with many other meticulous observers: there was no solid, conclusive proof that either contender had reached the Pole, but if only one had done so, it was more likely Cook. When the Congressional committee hearings terminated, Peary was endorsed, despite various conflicts in his testimony, and became recognized in most reference books as the discoverer of the North Pole. Cook, unanointed by the United States Congress, is hardly mentioned, as if he were being erased from history by proclamation.

During his later life, he wrote, lectured and traveled widely, working as an anthropologist, geologist and oil promoter. During his tenure as president of the Petroleum Producers' Association, he was indicted, found guilty and sentenced to fourteen years and nine months for stock fraud. While his supporters were maintaining that this was just a further penalty for disputing Peary's priority, and Cook was in prison denying his guilt, the "worthless oil lands" he had promoted brought in fairly large profits, sometimes running into the millions. He was paroled in 1930, and fully pardoned in 1940 — only a few months before he died of a cerebrovascular occlusion.

Although he never saw the total, public vindication of his past, if there was any truth to the old accusations of fraud, he died without a word of confession or remorse.

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

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CASE 42361

PRESENTATION OF CASE

A sixty-two-year-old man entered the hospital because of dyspnea.

Two weeks previously he noted the onset of exertional dyspnea that gradually progressed to dyspnea at rest. Subsequently, he became anorectic. During the five days before admission he had been febrile, with daily elevations of temperature to 102°F. associated with a cough that was productive of small quantities of blood-tinged sputum. There were no chills, pain, orthopnea or paroxysmal nocturnal dyspnea.

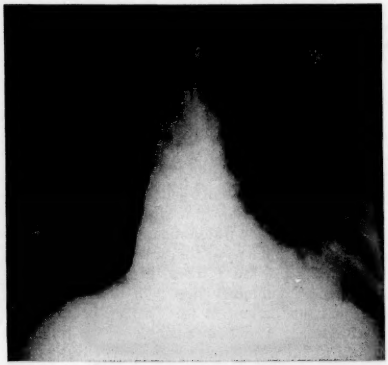

FIGURE 1. *Preoperative Film of the Chest, Showing the Chondrosarcoma of the Sixth Rib Overlying the Lower Portion of the Left Hemithorax.*

Ten months previously a large chondrosarcoma of the left sixth rib (Fig. 1 and 2) that had encroached upon the pericardial fat and the upper surface of the diaphragm was excised en bloc with the anterior portions of the fifth and seventh ribs. Postoperatively, there were episodes of dull, aching pain in the left buttock that radiated posteriorly down the thigh and leg and occurred mostly at night. X-ray films of the lumbar spine, pelvis, left leg and ankle were normal except for osteoarthritic changes in the lumbar spine and slight irregularity of the posterior surface of the upper portion of the tibia. Films of the chest taken four weeks and one week (Fig. 3) before entry demonstrated small segmental atelectasis in the left-lower-lung field and coarsened bronchovascular markings.

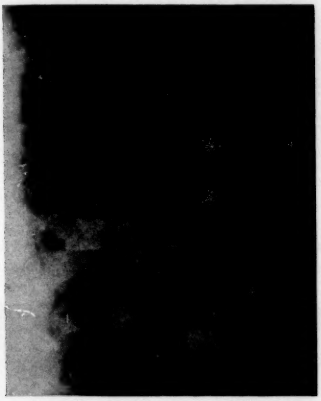

FIGURE 2. *Detailed View of the Left Sixth Rib, Showing the Expanded Destroyed Anterior Portion.*

Physical examination revealed an obese, cyanotic, dyspneic, apprehensive man. There was no distention of the veins of the neck. Examination of the chest showed a healed operative incision on the left. Medium moist rales were audible over both lower-lung fields. The heart was not enlarged. No murmurs were heard. The edge of the liver, which was smooth and tender, was felt 2 fingerbreadths below the right costal margin. The spleen was not palpable. There was no edema.

The temperature was 100.6°F., the pulse 90, and the respirations 36. The blood pressure was 130 systolic, 60 diastolic.

The urine was normal. Examination of the blood revealed a hemoglobin of 14.4 gm. per 100 ml. and a white-cell count of 9400. The nonprotein nitrogen was 30 mg., the calcium 8.8 mg., and the phosphorus 3.1 mg. per 100 ml. The sodium was 135 milliequiv., the chloride 105 milliequiv., and the carbon dioxide 23 milliequiv. per liter. The alkaline phosphatase was 4.7 units. The transaminase was 21 units. Cultures of the sputum grew out moderate alpha-hemolytic

streptococci and abundant yeasts; smears were negative for acid-fast bacilli. A blood culture was negative. Cytologic examination of three specimens of

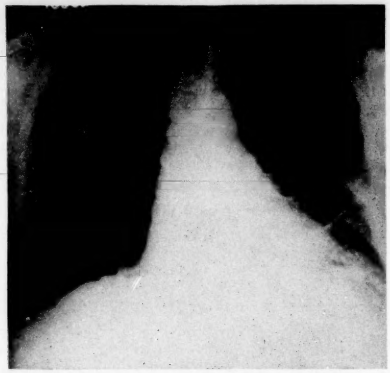

FIGURE 3. *Roentgenogram of the Chest One Week before Entry, Showing Linear Densities in Both Lungs, More Pronounced on the Left.*

sputum for malignant cells was doubtful; a fourth specimen was negative. X-ray films of the chest

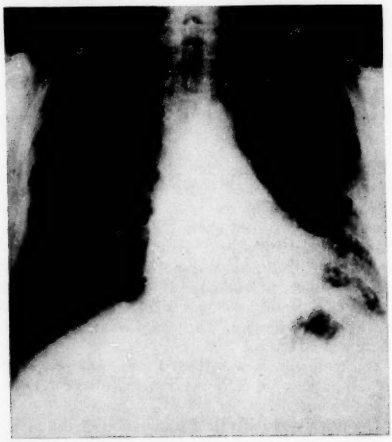

FIGURE 4. *Roentgenogram of the Chest on the Fourth Hospital Day, Showing an Increase in the Linear and Mottled Infiltrations in the Lungs.*

demonstrated multiple linear nodular densities scattered throughout both lung fields (Fig. 4). An electrocardiogram showed prolongation of the QT interval and borderline low T waves.

In spite of digitalis, Mercuhydrin and antibiotic therapy there was no improvement. The temperature ranged between 99.4 and 102°F. Films of the chest on the ninth hospital day showed the vascular shadows to be more pronounced and blurred; prominent, small, fluffy, round densities were noted in the peripheral lung fields; there was a questionable increase in

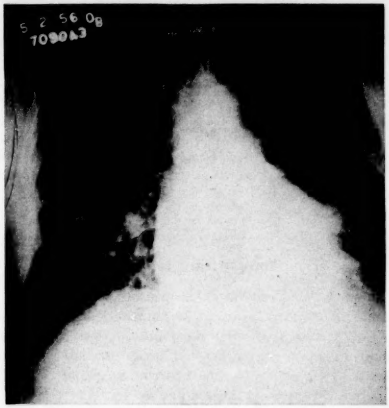

FIGURE 5. *Roentgenogram of the Chest Two Days before Death, Showing a Further Marked Increase in the Linear and Mottled Infiltrations in the Lungs.*

the size of the heart (Fig. 5). The patient died two days later.

DIFFERENTIAL DIAGNOSIS

DR. GEORGE LEVENE*: The principal complaint was dyspnea. Of course, dyspnea has many possible causes, but the most important can be classified under heart disease or pulmonary disease. The record says that the heart was not enlarged; there were no murmurs; the blood pressure was essentially normal; the pulse was 90, and the transaminase was normal. The only abnormal finding was the prolonged QT interval and a questionably low T wave. Prolonged QT intervals are most commonly due to a slow heart rate, which was not present in this patient, or to a prolonged systole. The best example of a prolonged systole is found with aortic stenosis. The history says that there were no murmurs. I wonder whether there was a systolic thrill at the base.

DR. BENJAMIN CASTLEMAN: There was not.

DR. LEVENE: Then I shall exclude diseases of the heart from serious consideration as a cause for the shortness of breath, though I do have a hunch that the patient had myocardial insufficiency of the type associated with slowly progressive sclerosis of the coronary arteries.

*Chief, Department of Radiology, Massachusetts Memorial Hospitals; professor of radiology, Boston University School of Medicine.

Included in the roentgenograms is a set of intravenous pyelograms. The history does not reveal why these were indicated, so I shall have to confine my observations to what I see on the films. The kidneys are normal in size, shape and position. Both psoas outlines are clear. I see no stones. The bladder wall is thickened, and there is a large pressure defect at the base produced by enlargement of the prostate. This looks like benign enlargement of the prostate, but it must be remembered that at least half the cases of carcinoma of the prostate are associated with benign prostatic enlargement. The alkaline phosphatase was normal. Was an acid phosphatase determination done?

DR. CASTLEMAN: I do not believe so.

DR. LEVENE: Then there is no evidence to incriminate the prostate other than to say that it was benignly hypertrophied.

After operation the patient complained of pain that radiated down the buttocks and the backs of the thighs. That sounds like pain produced by irritation of the nerve roots. It is not uncommon for patients to have backache after they have been on an operating table. Did this pain persist after operation?

DR. KATHERINE SPRENG: It was not noted especially, but he still had it a year later.

DR. LEVENE: I do not see enough in the x-ray films to account for that type of pain. There are osteoarthritic changes in the lower thoracic segments. The lumbar vertebras look normal; the lateral articulations are quite relaxed and widened and show considerable osteitic reaction. Some orthopedists would call them unstable lateral articulations, but I do not think they would cause the type of pain of which this patient complained. Films of the hips and pelvis show nothing significant. I see no bone disease.

Having excluded the heart as the primary cause of shortness of breath, I must consider the lungs. Whenever there is an unusual film of the lungs, the natural question to ask is whether it is due to infection or tumor. If this was infection the only one I should entertain for a moment is a bronchomycotic infection producing nodules, because all bronchomycoses, except actinomycosis and aspergillosis, produce nodular densities in the lungs. Yeasts were found in the sputum. Was *Candida albicans* found and isolated?

DR. SPRENG: I cannot answer with certainty because the finding of yeast in the sputum is not unusual and no significance was attached to that.

DR. LEVENE: Then I shall dismiss bronchomycotic infection. I do believe, however, that whatever else the patient had, he had persistent intercurrent respiratory infection, at times perhaps assuming the proportions of a bronchopneumonia, which responded to treatment.

The x-ray films taken ten months before admission show a tumor of the left sixth rib (Fig. 1 and 2), which proved to be chondrosarcoma. There is an area of density in the lower-lung field, which was interpreted as segmental atelectasis, though that density could well have been produced by the overlying tumor, since it involved the pericardial fat. In considering tumor as a possibility in the later illness, one must decide whether it was primary tumor or metastatic. As the findings evolved in films at later dates (Fig. 3, 4 and 5) many nodular densities suddenly appeared. If the tumor had been primary, it would have had to be of multicentric origin. The tumor that best fits that qualification is alveolar adenomatosis, which, of course, is an uncommon type of carcinoma of the lungs. I tell my associates and my students, when they are reaching out for fancy diagnoses, "Remember, the common things are more common." Following my own advice, I am inclined to exclude that as a possibility. Therefore, I must consider metastatic tumor.

This man had a chondrosarcoma of the rib. These tumors commonly metastasize to the lungs. The distinguishing feature of a chondrosarcoma roentgenologically, in addition to the evidence of expansion of bone, is that it contains little flecks of calcium. Metastases from chondrosarcoma resemble the original tumor in structure; therefore, if there are metastases to the lung from chondrosarcoma they should contain calcium. In looking at one of these films I see a shadow that was not present originally and that does seem to contain calcific densities. At this point the approach to the diagnosis becomes purely pragmatic. Is there calcium or is there not? It is difficult to recognize small calcific densities in the lungs without special technics like laminagraphy. I interpret some of these densities as calcium; therefore, I must conclude that the tumor was a metastatic chondrosarcoma and that there was associated intercurrent infection.

If the patient had metastases to the lungs, he may also have had metastases to the spinal cord, which may have caused the pain. The appearance of the heart interests me. The record states that the heart was normal. One of the most commonly accepted technics for estimating the size of the heart is the so-called cardiothoracic ratio of Danzer, which says that the transverse diameter of the normal heart should not exceed 50 per cent of the greatest internal diameter of the thorax. A few years ago I measured several hundred normal hearts and found that the average normal heart was 45 per cent of the internal diameter of the chest. I should not call a heart enlarged unless it is over 50 per cent. Any patient might have an increase in the size of the heart of at least 9 per cent before the radiologist could recognize the enlargement. In this patient we are fortunate enough to have films in which to compare the size of the heart. It has enlarged. Moreover, the superior vena cava and right innominate vein are markedly prominent; they were not visible on the original examination. Prominence of the superior vena cava and innominate vein suggests a high venous pressure. The record states that he did not have an elevated venous

pressure, but I should expect that by the time the last roentgenogram was taken, the venous pressure was high.

A prominent vena cava is seen in ventricular failure. This heart does not look like those seen in ventricular failure, because the cardiohepatic angle has become more acute rather than obtuse. There is no pleural fluid, and the bifurcation of the trachea, which shows very faintly on these films, is not widened. In ventricular failure there is widening of the angle of the carina. So, I must consider other possibilities to explain the prominence of these veins.

If there were metastases to the lungs, it is conceivable that a lymph node containing a metastasis pressed on the vena cava, or that a metastatic nodule had thrombosed the vena cava. I think that in either case, however, because of the resultant anoxemia of the heart, there would have been more evidence of heart failure than we see in the films.

One of the classic causes of prominence of the great veins is constrictive pericarditis. It is not beyond the realm of possibility that, as a result of the operation that involved the pericardium or as a result of seeding to the pericardium by metastatic tumor, an adhesive pericarditis developed. More commonly adhesive pericarditis, even though the primary disease may be on the left, is found on the right, for the amplitude of the heart beat on the left is great enough to separate the visceral and parietal layers of the pericardium and prevent the formation of synechiae.

Another possibility is pericardial effusion. This heart shadow has become larger; the atrioventricular sulcus has become obliterated, and the cardiohepatic angle has become acute. These are the roentgenographic changes of pericardial effusion. Of course, with pericardial effusion, when the intrapericardial pressure becomes great enough to produce cardiac tamponade the superior vena cava becomes prominent.

In summary I shall say that the patient had metastatic chondrosarcoma; that the lungs felt gritty on section; that there was an associated smoldering respiratory infection, at times reaching the magnitude of bronchopneumonia; that there was some involvement of the pericardium; and that there was benign prostatic hypertrophy.

DR. JAMES F. DONOVAN: I saw this man in consultation with Dr. Robert C. Coe, who did the original excisional operation. He was seen at the Orthopedic Clinic because of pain in the left buttock, and on the anterior side he had some pubic pain. We were greatly puzzled and admitted the possibility of metastases but could not prove it by x-ray examination of the pelvis. He was not a complainer and had undergone extensive tests before the first operation, with many negative results. It was evident that a progressive process was present; yet we could not put our fingers on it. Over a period of a week he went rapidly downhill and could no longer climb one flight of stairs because of dyspnea and fatigue. At that time, when I examined the chest I found no abnormalities. A week later there were questionable lesions in the chest on x-ray examination. It became increasingly difficult for him to breathe.

DR. CASTLEMAN: Dr. Hanelin, have you a comment on the x-ray findings?

DR. JOSEPH HANELIN: This case provoked a great deal of discussion at our conferences, for it presented a number of unusual features. Ordinarily, chondrosarcomas and sarcomas in general metastasize to the lungs through the hematogenous route. Then, we commonly see fairly discrete nodules in the lungs, rather than linear shadows, which one associates with a lymphatic spread of tumor. In addition hematogenous spread of tumor to lung is not generally accompanied by the amount of dyspnea that this man had. The rapidity of the development of the process was disturbing. In a few days there were marked changes in the lungs. These features suggested some unconventional process.

DR. MADAN SINGH: When the patient was first admitted to the hospital we had no doubt about the diagnosis. Obviously, it was chondrosarcoma metastatic to the lung. Impressed by the rapidity of onset and progression of dyspnea and radiologic changes in the lungs, we presented this case at the Thoracic Rounds, only to find out that we were living in a fool's paradise. It was pointed out that the chances that this was metastatic chondrosarcoma were exceedingly unlikely. From then on, we did not know what we were dealing with.

DR. DONOVAN: Dr. Barr, have you ever seen metastatic chondrosarcoma produce a pulmonary picture like this in a period of weeks?

DR. JOSEPH S. BARR: No, I never have; it is usually a slower process. I was impressed, though, with the fact that this was a local lesion; it may have been seeded locally and thus have a different appearance in the films from that seen in cases with hematogenous spread.

CLINICAL DIAGNOSIS

?Chondrosarcoma, metastatic, to lung.

DR. GEORGE LEVENE'S DIAGNOSIS

Chondrosarcoma, metastatic, to lung.

ANATOMICAL DIAGNOSES

(Chondrosarcoma, of rib), with extensive intrapulmonary vascular metastases.
Cor pulmonale.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Autopsy showed that the patient had metastatic chondrosarcoma of the lung. When chondrosarcoma does metastasize to the lung (and it

usually does) it usually produces nodules, but the metastases are almost always by the venous and not the lymphatic channels. In this case the nodules were white and glistening and were linear in deposition, because they were in the pulmonary arteries, which were plugged with tumor (Fig. 6 and 7). There was no large tumor mass in the parenchyma; in fact there was no tumor in the parenchyma at all except for the small amounts that extended through the pulmonary arteries. We did not notice any calcium, but it is possible that it was present. Since Dr. Levene has used that as a criterion in making the diagnosis, we shall do a calcium stain on some of the sections. I reviewed the microscopical slides of the original tumor of the rib and was able to find tumor in an intercostal vein, from which I believe the tumor metastasized to the lungs. When the spread occurred is problematical. It is possible that the manipulation during the removal of the tumor caused some of the tumor thrombi in the intercostal veins and its radicles to migrate to the lungs, where they remained latent for a while and then started to grow. The fact that it grew so rapidly in a short period may mean that the tumor cells were

FIGURE 6. *Cross-Section of the Lung.*
The white areas are chondrosarcoma-filled pulmonary arteries.

quiescent for about ten months, and then for some reason, suddenly began to grow at a rapid rate.

The involvement of so many of the pulmonary arteries by tumor led to a cor pulmonale. The right side of the heart was hypertrophied to about twice the normal size. Years ago Brill and Robertson[1] described this condition as subacute cor pulmonale — that is, when the metastatic carcinoma involved the vessels rather than the more commonly involved lymphatics. Some years ago we had a case exactly like this, in which the metastases were in the pulmonary vessels. Lichtenstein and Jaffe[2] reported that chondrosarcoma usually metastasized to lung via the venous channels and not the lymphatics.

DR. LLOYD H. SMITH: Did you find any thrombi in the veins in the legs?

DR. SPRENG: While the patient was in the hospital it was believed that there was an infection to the thigh from the intercurrent infection and that the pain in the legs was not related to the disease.

FIGURE 7. *Photomicrograph, Showing Chondrosarcoma-Filled Pulmonary Arteries.*

A PHYSICIAN: In the cases described by Jaffe and Lichtenstein was the primary site of the tumor in the ribs?

DR. CASTLEMAN: I do not know. Most of the complications of chondrosarcoma of the ribs that we have seen have been due to local recurrence with spread to the pleural cavity. In those cases there were large masses of chondrosarcoma. In the case under discussion there was no residual disease at the site of the original tumor.

DR. LEVENE: Ackerman and del Regato[3] state that chondrosarcomas of the ribs frequently metastasize to the lungs through the intercostal veins. Two chondrosarcomas of the ribs were presented here — 1 in 1933[4] and 1 in 1938.[5] At one of those conferences Dr. Churchill[5] said that chondrosarcomas of the ribs were among the most treacherous tumors that he knew.

DR. CASTLEMAN: I think that Dr. Churchill was probably referring to the need for radical surgical

treatment. The surgical treatment now is to remove the entire rib; with large lesions a local excision is usually not sufficient, for there may be repeated recurrences, which eventually cause the patient's death. In the patient under discussion the whole rib was removed en bloc; the operation apparently was successful because there was no local recurrence.

DR. SPRENG: Was there any evidence of superimposed infection in the lungs?

DR. CASTLEMAN: No.

DR. BARR: We have had similar experience with chondrosarcomas in the pelvis. The rule now is that if excisions are attempted, the whole bone that is involved must be removed, which in chondrosarcoma of the ilium — a very common location — means a hindquarter amputation.

DR. CASTLEMAN: Most of the hindquarter amputations for chondrosarcomas of the ischium or any of the bones in the pelvis have resulted in cures.[6]

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CASE 42362

PRESENTATION OF CASE

A forty-four-year-old woman entered the hospital because of a draining sinus in a surgical incision over the left buttock.

Five years previously while gardening she noted a "back strain." Since then episodes of nonradiating pain in the middle portion of the lower back occurred when she was fatigued. Six months before admission there was severe pain in the back that radiated down the left buttock, the posterior aspect of the left thigh and the calf. At times paresthesias were noted along the lateral portion of the left foot. The pain persisted in spite of codeine and aspirin, which afforded some relief. At times the ankle jerk was absent on the left. Otherwise, the ankle and knee jerks were active and equal bilaterally. Straight-leg raising was limited to an angle of 45° on the left; the right leg could be extended 60°. Flexion of the left hip, which reproduced the pain in the back, was limited to 110°. Except for possible slightly diminished sensation to pinprick over the lateral area of the left foot, sensation was not impaired. There was no loss of motor power in the toes. X-ray films of the lumbar spine and pelvis demonstrated some narrowing of the fourth and fifth lumbar intervertebral disks; there was sclerotic change along the apophyseal joints between the fourth and fifth lumbar and between the fifth lumbar and first sacral vertebras; there was minimal spurring along the lumbar bodies; a spina bifida of the first sacral segment with a floating spinous process was present; calcified lymph nodes were noted on the left side of the abdomen. With five weeks of rest in bed there was no relief of symptoms.

Four months before entry a myelogram showed a small cystic outpouching measuring 0.5 by 1.0 cm. on the left at the level of the fifth lumbar vertebra; the remainder of the spinal canal appeared normal; colorless, slightly cloudy, acellular spinal fluid was obtained; the total protein was 62 mg. per 100 ml., and a Hinton test was negative. Two and a half months before admission fusion of the fourth and fifth lumbar vertebras to the sacrum with a graft from the left ilium was performed. During the first postoperative week the temperature ranged between normal and 102.6°F., with daily chills in the late afternoon associated with headaches. The white-cell count ranged between 3400 and 6500. Blood cultures and a Widal agglutination test were negative. Examination of the blood for malarial parasites was negative. Chloromycetin therapy was given between the second and fourth postoperative days. After the seventh postoperative day the temperature was normal. An abscess in the region of the donor site with a subsequent draining sinus was noted. Several weeks before entry, pain recurred in the left thigh and leg.

FIGURE 1. *Roentgenogram of the Pelvis, Showing Increased Radiolucency, Poorly Defined, along the Left Sacroiliac Joint (Arrows).*

Physical examination showed a well nourished woman. There was a draining sinus over the left buttock at the inferior end of an otherwise healed surgical incision that was the donor site of the iliac graft. The left-ankle jerk was absent.

The temperature was 98°F., the pulse 88, and the respirations 20. The blood pressure was 135 systolic, 80 diastolic.

The urine gave a + test for albumin. Examination of the blood revealed a hemoglobin of 11.8 gm. per 100 ml. and a white-cell count of 5200. X-ray films of the pelvis showed the outline of the fifth lumbar vertebra to be indistinct. There was increased radio-

lucency of the left ilium along the sacroiliac joint (Fig. 1).

An operation was performed on the second hospital day.

Differential Diagnosis

Dr. Joseph S. Barr*: May we see the films?

Dr. Joseph Hanelin: I do not have all the films here; those made before the first operation are missing. In the films taken before the second operation there is some suggestion of abnormality. On the left the margin of the medial aspect of the ilium, as it overshadows the sacrum, is indistinct, and as a result the sacroiliac-joint space appears wider than normal; the sacral margin itself seems to be well defined (Fig. 1). Unfortunately, this area is considerably obscured by gas and fecal material in the colon.

Dr. Barr: Do you see the iliopsoas shadows?

Dr. Hanelin: They are obscured also.

Dr. Carter Rowe: The sacroiliac joints and the muscles were interpreted as normal in the films taken before the operation. The only abnormality noted was marked hypertrophic change of the facets of the fourth and fifth lumbar vertebras on both sides. The plain films without gas in the bowel were interpreted as normal.

Dr. Hanelin: After the first surgical procedure one can see in the lateral film the graft lying between the spinous processes of the fourth lumbar and second sacral segments. The indistinct margin of the fifth lumbar vertebra may be due to the overshadowing bone graft. The lungs are clear; the heart size is within normal limits. The lateral film of the chest shows the thoracic spine, which also seems to be normal.

Dr. Barr: This patient had a characteristic story of low-back strain followed by repeated episodes of low-back pain and then finally that which all patients dread, pain down the leg in a pattern characteristic of sciatic distribution, with paresthesias on the lateral border of the foot. When there are paresthesias on the lateral border of the foot with this syndrome we are fairly confident that the root of the first sacral nerve has been involved in an irritative process. It is quite common for physicians on just that much evidence to assume that a lesion of the disk is present and to proceed with operative treatment. But we must remember that there are many causes for radiating pain other than lesions of disks. The ankle jerk was absent at times and was present at other times. This suggests again an irritative lesion rather than severe pressure on the root. Later on, the ankle jerk had disappeared completely. Straight-leg raising was limited to 45° on the left and 60° on the right. Flexion of the hip produced pain in the back and was limited to 110°. That is a most unusual finding. If the lesion is in the lumbosacral spine, hip flexion alone should be normal. Changes in the apophyseal joints are noted in the protocol. I am not too certain about them as I look at the films; I should like to see lateral views without so much gas in the abdomen. After the operation the changes in the lateral view are minimal; there is only mild sharpening of the edges of the vertebras; perhaps one would normally expect such changes in a forty-four-year-old woman who had done some gardening. Did the patient live in this part of the country, and had she always lived here?

Dr. Rowe: Just before the first operation she had been to the West Indies for six weeks; she lived in this area.

Dr. Barr: The small outpocketing seen in the myelogram, I suppose, was a congenital dural cyst and perhaps of no significance.

Dr. Hanelin: I should think so.

Dr. Barr: The total protein was elevated, but no evidence of an intradural lesion was reported in the myelogram. A spinal fusion was done, apparently without exploration.

Dr. Rowe: The spine was examined; there was no rupture of the disk.

Dr. Barr: I had hoped that that was the case. None of us would like to do a spinal fusion in a patient who had or had had radiating sciatic pain without being certain that the nerve roots in that area were free from pressure.

Then the patient had some elevation of temperature with chills. The physicians obviously were not certain about a pyogenic infection, for Chloromycetin was used but, I gather, only for two or three days. The abscess apparently developed spontaneously, and the drainage was spontaneous.

Dr. Rowe: Actually, there was puckering of the skin about the graft incision, which later became a small area of granulation and then slowly developed into a sinus. There was never real abscess formation and discharge of pus.

Dr. Barr: Was Bence-Jones protein looked for?

Dr. B. Cohen: It was absent.

Dr. Barr: After reading the protocol I listed various diagnoses, most of which I can easily exclude. The patient was too old for Ewing's sarcoma, and the type of destruction was not that which one might expect in such a lesion. The same thing is true of multiple myeloma. The dural cyst that was noted in the myelogram is supposed to have some connection with back and leg pain in some patients. I, personally, have not seen a case in which I thought that was the whole answer. I believe that in the patient under discussion it was just a congenital variation.

A foreign body in the operative wound is another possibility. If a sponge is left in the wound, an abscess forms and drains. I shall exclude that.

There may have been postoperative sepsis in a hematoma. When I read about destruction in the body of the fifth lumbar vertebra I wondered if perhaps there had been postoperative sepsis with drainage toward the ilium. If both tables of the ilium

*Chief of Orthopedic Service, Massachusetts General Hospital.

had been removed the abscess might point over the buttocks, but I assume that only one table was used in removal of the graft.

Finally, I raise the question of tuberculosis of the sacroiliac joint, and I shall conclude my discussion, for I think that is probably the answer to this problem. Were there tuberculin tests of the skin?

DR. ROWE: On the second admission they were positive.

DR. BARR: Was there a family history of tuberculosis?

DR. ROWE: No.

DR. BARR: I think that tuberculosis explains the story reasonably well. The patient had a lesion that had been present for some time and had produced irritation of the lumbosacral plexus, with pain radiating down the left leg. After the operation a sinus developed. The process obviously was not acute. It developed gradually, with an indolent granulation reaction. We see very few patients with tuberculosis of the sacroiliac joint nowadays; as a matter of fact, we see very little tuberculosis of the bones and joints. I think this picture is characteristic of an infectious process — haziness of the joint space, lack of the normal subchondral bone and even the tendency to formation of excessive amounts of gas in the abdomen.

DR. BENJAMIN CASTLEMAN: Dr. Hanelin, do you agree that that is consistent with tuberculosis?

DR. HANELIN: Yes; although from the destruction alone I should hesitate to exclude other possibilities, both infectious and neoplastic, the course would fit an infectious process best.

DR. ROWE: This case was a puzzling one. I had followed the patient for several years because of back and leg pain. Although she tired easily, her general physical condition was good; yet she had persistent disabling back and leg pains; the leg pain was not as severe as the back pain. I am sorry that we have not the preoperative films taken before the fusion. She had been of little use economically for two or three years. We thought we might help her by eliminating motion at the fourth and fifth lumbar and first sacral facets of the spine by fusion. We did not expect to find a ruptured disk. On exploration the dura and the posterior longitudinal ligament appeared normal. The facets were badly spurred with hypertrophic changes, so we fused the spine from the fourth lumbar to the sacral vertebra.

During the first week postoperatively because she had a low-grade fever we thought that there was sepsis in the wound, but the wound looked all right and the white-cell count was not elevated but depressed. Soon afterward a small red area appeared and grew larger but was never very disturbing. She was sent home. While she was at home the sinus opened up gradually. We thought it was a reaction to a foreign body. I thought that I had possibly left a sponge in the wound. I did not expect sepsis because it did not act like sepsis.

A PHYSICIAN: Has the sciatic pain disappeared, Dr. Rowe?

DR. ROWE: She has occasional mild discomfort.

CLINICAL DIAGNOSIS

Foreign-body reaction.

DR. JOSEPH S. BARR'S DIAGNOSIS

Tuberculosis of sacroiliac joint.

ANATOMICAL DIAGNOSIS

Tuberculosis of sacroiliac joint.

PATHOLOGICAL DISCUSSION

DR. ROWE: When I exposed the sinus, the graft site, except for granulations, appeared perfectly normal. We were unable to find foreign material. Because of the changes in the films taken on the morning of operation, I explored the inner side of the graft site and fell into a pocket. As we examined that pocket it became obvious that the whole sacroiliac joint was full of necrotic bone and cartilage. The area was curetted, packed and left open.

DR. CASTLEMAN: The biopsy proved that this material was tuberculous. There was no doubt about the diagnosis of tuberculosis; this included a positive guinea-pig test.

DR. ROWE: The wound closed up within two months. The patient has improved a great deal on specific chemotherapy and rest; much of the pain has diminished.

DR. CASTLEMAN: Do you think that the spinal lesion had any part in producing the pain?

DR. ROWE: I did not see any suspicious areas of destruction or infection at the time of the first operation. I think that the changes in that area in the x-ray film are produced by the bone grafts. The symptoms were most probably produced by tuberculosis of the sacroiliac joint.

DR. HANELIN: The joint looks well preserved in the lateral film.

DR. CASTLEMAN: Do you think that all the symptoms were due to the tuberculosis of the joint?

DR. ROWE: Lesions of the sacroiliac joint can simulate those of irritation at the fourth to fifth lumbar roots.

DR. BARR: I should like to say, for the benefit of the students who have not seen this type of lesion, that before the days of antibiotics tuberculosis of the sacroiliac joint carried a very high mortality — 30 to 50 per cent. Draining sinuses usually developed and became secondarily infected. Then, amyloid disease occurred, with deposits in the liver, spleen and kidneys; the patient became cachectic and finally died. With prompt recognition, antibiotics and surgical exenteration of the lesion the prognosis is different; the patient has a good prospect of being perfectly well.

The New England
Journal of Medicine

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY

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REGARDING PERIODIC REGISTRATION OF PHYSICIANS

FOR ten years the Council of the Massachusetts Medical Society has been debating periodically whether or not physicians should be required to re-register periodically. With one exception (and that vote was later rescinded) the debate has been won by the physicians opposed to registration renewal.

The question has also been debated many times in the General Court of the Commonwealth of Massachusetts, the most recent debate being over House Document 1639, filed this session to provide for the biennial renewal of the registration of physicians. H. 1639 passed the House in June, and in the course of legislative procedure was referred by the Senate to the Senate Ways and Means Committee. This committee, however, believing that the subject of H. 1639 and other matters on its agenda were worthy of additional study, requested that it be authorized to sit during the recess of the General Court to study those yet unsolved problems. The General Court so voted.

Proponents of periodic renewal of the registration of physicians argue that once a physician is registered by the Board of Registration in Medicine, he remains, unless his license is revoked by the Board, forever so registered. No changes of his address are kept by the Board, and whether or not a registered physician is still in active practice is not indicated in the Board's files.

Periodic registration, proponents point out, would provide an up-to-date list of duly licensed and qualified physicians in practice in the State. Such a list would be of particular value for civil-defense purposes, and would be of help in tracking down persons illegally practicing medicine. It has also been argued by proponents that periodic re-registration would bring in additional funds to the Board of Registration in Medicine — funds needed for additional personnel and salary increases. That other professional groups are required to re-register periodically without any apparent burden or grief has also been used as an argument that physicians could do likewise.

Opponents of registration renewal argue that re-registration fees collected would not necessarily be turned over to the Board of Registration in Medicine, since all monies taken in by the Board go into the general fund and the Board operates under an annual appropriation. The argument of the proponents that an up-to-date list of practicing physicians would deter the illegal practitioner from his self-appointed rounds, the opponents believe, is not sound, since persons posing as physicians will have no more concern over periodic renewal than they have over initial examination and registration.

If the Board wishes to increase its policing activity (as contrasted to its legislated responsibility of examining and licensing of physicians), such activity, say the opponents, should be financed by the public that benefits by protection. And, if periodic re-regis-

tration is for civil-defense purposes, this cost, too, should be met by the general public.

In a letter to the chairman of the Senate Committee on Ways and Means, Dr. Lawrence R. Dame, of Greenfield, long an opponent of re-registration and a member of the Society's Committee on State Legislation, asserts that compulsory periodic re-registration is actually an occupational tax. He writes that he is "awed and irked" in his concentration on his practice by the "many additional legal and paper requirements bearing on a physician from the increasing State and Federal divisions." Dr. Dame concludes his letter with this salient point: "If any medical case should be brought to Court for settlement, and it can be demonstrated that the physician was not legally re-registered at the time treatment was given, legal argument can be introduced to settle the case by decision of the Judge on the grounds that the physician was illegally practicing medicine at the time."

That other professional groups are required to re-register, opponents state, is no argument and they point out that, by and large, such legislation to re-register these groups was effected after voluntary application from them for periodic re-registration.

On February 3, 1954, the Council voted that a committee of the Society be appointed to study the desirability of any needed changes in the administration of the registration of physicians. This committee may come up with a happy compromise.

In the meantime the debate continues.

SILENCE, LIKE A POULTICE—

One thing that technology with its factory whistles, sirens, motor horns, telephone and other bells, agents of transportation, typewriters, adding machines, subtracting machines, machine guns and engines in general has failed to produce on any significant scale is silence. And with reference to noise, the classical antonym of silence, even a mention of the subject automatically raises the question why radio announcers, in plugging a product to their friends the nation over, find it necessary to talk not only faster but louder as their time approaches its blessed end. In any consideration of silence or of noise the human voice should not be neglected.

That silence is, or has been, appreciated is attested by the literary allusions that have been made to it. In the index to *Bartlett's Familiar Quotations,* 1937 edition, for example, no less than 10.5 inches of 6-point type is required for listing of the literary references to silence, 0.5 inches to silences, 0.125 to silenced, 7 to silent and 0.25 to silently, a grand total of 18.375 inches — approximately 46 centimeters — representing 170 separate items.

The references themselves range from Silence, a time to keep, through Silence, give me but, Silent dark o'ershadowing tomb and Silent upon a peak in Darien, to Silently steal away. The poets, at least, appreciated silence.

It is encouraging to note that Science, also, which has been responsible for so much noise, is now about to turn its attention to the problem that has been thus created. On September 17 at the Yale–New Haven Medical Center, in Connecticut, a one-day symposium on occupational noise is to be held that will cover all angles of the subject, from the physiologic and psychologic to the economic and legal, including, it may be hoped, the radio announcer in the throes of plugging a product.

The symposium will be held under the joint sponsorship of the Yale School of Medicine, the Grace–New Haven Hospital and the Liberty Mutual Insurance Company, and it is expected that much will come of it, in a quiet way.

ACADEMIC MIGRANTS

The annual reception tendered in July by the American Academy of Arts and Sciences to foreign scholars enrolled in the summer courses at Harvard and the Massachusetts Institute of Technology brought forth some hundred of these visitors. A subtle compliment was implied in their designation as scholars rather than as students, for whereas all scholars presumably remain lifelong students, considerably fewer students can in all conscience be called scholars. "Student" is an inclusive term applied to a learner or one who merely attends a school (a scholar in this sense at least). A scholar is "one who has engaged in advanced study and acquired knowledge in some special field." He might be characterized even better as one "learned and still learning."

Opportunely in relation to the occasion sponsored by the Academy was the almost simultaneous release by the Institute of National Education of the annual census of American and foreign educational exchanges. The census is based on data published in the Institute's booklet, *Open Doors,* relative to nearly 55,000 learned and learning persons who have traveled between the United States and foreign countries in the academic year 1955 to 1956 for the general purpose of education.

The figures collected show that 43,309 foreign citizens were in this country for educational purposes in 1955-56; 36,494 of them were students and perhaps scholars, 6033 were doctors and 782 were teachers and research workers. Of this foreign personnel 13,301 came from the Far East, 9,879 from Latin America, 7,336 from Europe, 5,667 from other countries of North America, 5,358 from the Near and Middle East, 1,315 from Africa and 419 from Oceania. Coming from 132 nations and political areas these students were distributed among 1630 institutions of higher education. Interestingly enough,

Greece, with 962 students, contributed the largest national European group. The six institutions receiving the greatest numbers of students were, in order, the University of California with 1392, Columbia University with 1224, the University of Michigan with 1070, New York University with 776, Harvard with 729 and Massachusetts Institute of Technology with 658. In medicine 6033 foreign physicians from 84 countries trained in 764 hospitals in the United States, an increase of nearly 1000 over the previous year.

Figures are not complete for United States citizens studying abroad in the academic year recently ended, but in 1954-1955 there were 9457 who studied at 388 institutions in 49 foreign countries and political areas. Fifty-nine per cent of these were in Europe, 16 per cent in Latin America and 15 per cent in Canada. Canada had the largest number with 1441, closely followed by Mexico, the United Kingdom, France, Germany and Switzerland. Inadequate information indicates that at least 22 per cent of the Americans abroad studied in the humanities and 18 per cent in medicine.

There was a time, in this young country, when students desiring advanced education turned their faces eastward. In no branch of learning was this more evident than in medicine. The balance was struck in the present century and now the cultural progress of the western hemisphere and the debilitating effect on the Old World of wars and economic distress have caused the tide to set the other way.

Still it must not be forgotten, in the pride and boisterous arrogance of a still youthful nation that its own cultural roots remain buried deep in the civilizations from which it sprang. American inventiveness itself, born of necessity, and the boast of American technology, has tended to become crystallized in the ingenuity of the assembly line and reduplication without end. There are other things in life than production by automatism.

Even as foreign students flock to American institutions to study — *mirabile dictu* — the humanities and social sciences as well as engineering, the strong trend toward materialism can still not be denied. The lines of Wordsworth, written during the industrialization of England, must all the more be borne in mind, lest "getting and spending," we, too, risk laying waste our spiritual powers.

Could one of the Fathers in Medicine be present at any of our professional meetings in these days, he certainly would be entirely unable to comprehend the language used.

Boston M. & S. J. *September 11, 1856*

MASSACHUSETTS MEDICAL SOCIETY

STATED MEETING OF THE COUNCIL

A stated meeting of the Council will be held in John Ware Hall, Boston Medical Library, 8 Fenway, Boston, on Wednesday, October 3, at 10:30 a.m. This meeting will be followed by the Cotting Luncheon.

Business:

1. Call to order at 10:30 a.m.
2. Presentation of record of meeting held May 21, 1956, as published in Vol. 255, Supplement No. 1, July 5, 1956, of the *New England Journal of Medicine*.
3. Reports of standing and special committees.
4. Such other business as may legally come before this meeting.

ROBERT W. BUCK, M.D.
Secretary

COMMITTEE ON MATERNAL WELFARE

PULMONARY EMBOLISM AND SUPPURATIVE ENDOMETRITIS

A thirty-four-year-old gravida IV, para IV (one of twins) had mild essential hypertension and a history of delayed post-partum bleeding in her previous pregnancies. She made only three visits for prenatal care, and the last two of these were three weeks apart when by calculation she was overdue. Labor began spontaneously six weeks past the estimated date of confinement, and after about five hours' sedated labor, under spinal analgesia, a living infant, weighing 2.9 kg. (6 pounds, 9 ounces), was delivered uneventfully. The first post-partum day was uneventful, but on the second day the patient was restless, complaining of soreness in the pelvic area and headache, with a temperature of 101.4°F. The blood pressure on admission had been 190 systolic, 120 diastolic, and after delivery was 154 systolic, 100 diastolic. A blood culture was taken, and later reported as showing "beta-hemolytic streptococcus." On the third post-partum day she complained of tenseness in the neck, headache and soreness in the lower abdomen. She was "highly nervous." The temperature on this day was 103.4°F. Seen by a consultant at 11 o'clock in the morning of that day, she was started on intramuscular and oral administration of Tetracyn, intravenous infusion of fluids and codeine. The temperature had begun to respond, but at 4:15 p.m., without additional complaints or warning, she suddenly died.

Autopsy showed a large pulmonary embolus and acute suppurative endometritis.

This case was classified as caused by pulmonary embolus secondary to acute endometritis and puerperal sepsis, but its preventability was undetermined.

Although there is no doubt that a sudden massive pulmonary embolus is nonpreventable, from the practical point of view, one cannot escape the fact that the thrombi in the pelvis from which this embolus originated were due to puerperal sepsis. This should be in itself completely preventable today and constitutes therefore an unfortunate and preventable factor. The record implies, however, that the patient did not co-operate in early ambulation because of her previous experiences with post-partum hemorrhage. Therefore, she must bear some of the blame for the fact that profound stasis in the pelvic circulation supervened. On the other hand one wonders how vigorously she was encouraged or compelled to get out of bed and move around. These matters are theoretical, but bear some profitable thinking.

Another comment should be made regarding the patient's prenatal care. The scarcity and wide intervals of office visits from the thirty-seventh to forty-sixth weeks are deplorable and indeed completely inexcusable. Such negligent conduct of a pregnancy is the more reprehensible in view of the patient's known essential hypertension and a known tendency to hemorrhage. The explosive possibilities inherent in this combination should be too well known to need further emphasis, but include at least the following: eclampsia; toxic separation of the placenta; antepartum hemorrhage; afibrinogenemia; intra-uterine fetal death; bilateral cortical necrosis of the kidneys; and intracranial hemorrhage.

Although it is true that this patient — largely by sheer good luck — did not become involved in any of the complications noted, only to die of a probably nonpreventable disorder later on, the fact that she was inordinately exposed to these hazards must not be overlooked. Visits should have been demanded at the very least once a week beginning at the thirty-sixth week and toward the end, when she went beyond the expected date of confinement, probably two or three times weekly.

JOHN FIGGIS JEWETT, M.D.
Chairman

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR JULY, 1956

RÉSUMÉ

DISEASE	JULY 1956	JULY 1955	SEVEN-YEAR MEDIAN
Brucellosis	1	1	2
Chancroid	2	2	1
Chicken pox	636	531	439
Diphtheria	0	2	2
Dog bite	1520	1330	1404
Dysentery, bacillary	1	11	10
Encephalitis, infectious	0	1	2
German measles	413	86	121
Gonorrhea	193	189	186
Granuloma inguinale	2	0	0
Hepatitis, infectious	24	50	11
Lymphogranuloma venereum	1	0	0
Malaria	0	0	4
Measles	209	501	611
Meningitis, meningococcal	6	9	4
Meningitis, Pfeiffer bacillus	2	1	2
Meningitis, pneumococcal	2	3	2
Meningitis, staphylococcal	1	0	0
Meningitis, streptococcal	1	0	0
Meningitis, undetermined	5	5	4
Mumps	306	348	442
Poliomyelitis	15	419	64
Salmonellosis	89	32	12
Scarlet fever	124	110	106
Syphilis	208	174	140
Trichinosis	3	2	2
Tuberculosis, pulmonary	214	233	221
Tuberculosis, other forms	4	12	13
Typhoid fever	1	1	1
Whooping cough	46	70	126

COMMENT

Diseases below the seven-year median were diphtheria, bacillary dysentery, measles, mumps, poliomyelitis and whooping cough.

For only the second time (1952 also) in the history of the State, no cases of diphtheria were reported during the month of July.

With but one exception (1953) measles was at the lowest level during the month of July in the State's history.

Poliomyelitis was at the lowest level for the month of July since 1948, while whooping cough reached the lowest level for this month in the State's history.

Diseases above the seven-year median were chicken pox, German measles, infectious hepatitis, salmonellosis and scarlet fever.

During the month of July, salmonellosis reached the highest reported level in the State's history. However, nearly half the cases were accounted for by an outbreak among patients and personnel at a Boston hospital. The organism was found to be *Salmonella heidelberg*, and the source was thought to be an asymptomatic food handler from whose stool this same organism was isolated.

GEOGRAPHIC DISTRIBUTION OF CERTAIN DISEASES

The following diseases were reported from the communities named:

Brucellosis: Woburn, 1.

Dysentery, bacillary: Medford, 1.

Hepatitis, infectious: Agawam, 1; Amherst, 1; Arlington, 1; Auburn, 1; Boston, 3; Cambridge, 2; Clinton, 1; Danvers, 1; Fall River, 1; Gardner, 1; Greenfield, 1; Lexington, 1; Lowell, 1; Northampton, 2; Springfield, 1; Taunton, 1; Worcester, 1; Wrentham, 3; total, 24.

Meningitis, meningococcal: Arlington, 1; Falmouth, 1; Holyoke, 1; Quincy, 1; Webster, 1; Westwood, 1; total, 6.

Meningitis, Pfeiffer bacillus: Amherst, 1; Dedham, 1; total, 2.

Meningitis, pneumococcal: Somerville, 1; Worcester, 1; total, 2.

Meningitis, staphylococcal: Wayland, 1.

Meningitis, streptococcal: Worcester, 1.

Meningitis mumps: Malden, 1.

Meningitis, undetermined: Haverhill, 1; Marlboro, 1; Medford, 1; Newton, 1; Swampscott, 1; total, 5.

Poliomyelitis: Auburn, 1; Bolton, 1; Everett, 1; Gardner, 1; Greenfield, 1; Lowell, 1; Malden, 1; Medford, 1; Salem, 1; Shrewsbury, 2; Sutton, 1; Wellesley, 1; Worcester, 2; total, 15.

Rocky Mountain spotted fever: Bridgewater, 1.

Salmonellosis: Billerica, 2; Boston, 45; Braintree, 1; Brockton, 3; Brookline, 1; Framingham, 5; Greenfield, 1; Groton, 1; Hudson, 1; Lanesboro, 1; Lincoln, 2; Lowell, 3; Lynn, 1; Malden, 2; Marblehead, 2; Medford, 1; Melrose, 1; Northampton, 3; Revere, 1; Saugus, 1; Springfield, 3; Swampscott, 1; Topsfield, 2; Wakefield, 1; Weymouth, 1; Worcester, 3; total, 89.

Trichinosis: Boston, 3.

Typhoid fever: Springfield, 1.

CORRESPONDENCE

REGARDING THE PRESIDENT'S HEALTH

To the Editor: Apropos of Dr. Le Compte's letter in the *Journal* of August 2, 1956, about the variable reports upon the recent illnesses of President Eisenhower, the optimism of Dr. White is quite justified by the following facts:

1. The President's originally good general condition.
2. His prompt recovery and steady convalescence.
3. The very chronicity of his ileitis.
4. Having become familiar with the duties of his office, he should find them less exacting.
5. Continued activity on his part is highly desirable.
6. Optimistic prognoses are therapeutically helpful.

Those of us who, from necessity, convenience or choice, have treated most of our patients with coronary-artery disease at their homes and learned from personal experience the safety of relatively early ambulation and the resumption of work, fully appreciated the optimistic attitude of Dr. White.

GILBERT W. HAIGH, M.D.

Worcester, Massachusetts

BOOK REVIEW

Fear Strikes out. By Jim Piersall and Al Hirshberg. 8°, cloth, 217 pp. Boston: Little, Brown and Company, 1955. $3.50.

An attack of mental illness, even if it were available for the asking, is not usually recommended as desirable preparation for professional success. There is evidence that the behavior of Jim Piersall, the Boston Red Sox ballplayer, during part of his psychotic illness, as well as various aspects of his comeback, have been of distinct advantage in his career.

Fear Strikes out is a brief story, in the first person singular, of Piersall's life through 1954, when he had been recovered for two years from a psychotic episode. As every Red Sox fan knows, he had returned to that team and has, ever since, continued his brilliant performance as an extraordinary player. The writing in this book — how much is Piersall and how much Hirshberg, I do not know — is direct and simple and surely holds interest for supporters of Piersall and the Red Sox.

I have the impression that Piersall is a fortunate young man. In the first place, he had outstanding athletic ability, natively or owing to the early training and influence of his father, or both. Then impelling, persistent, impatient ambition and the balking of this by economic responsibility and strain, further than his perspective at that age could tolerate, seem to have been factors in propelling him into a gradually increasing mania. His potentialities and personality gained him the best of care and consideration in illness and convalescence. When he returned to playing baseball he had increasing success and had what was largely advantage in being already widely known and appreciated by fans for his clownish antics on the diamond in the days before his illness was recognized. Then come the gratification and exciting reward of writing and seeing published a book about himself. And now, I understand, a motion picture based on the book is to be made. A good part of this history suggests meat and drink for the ego, and one is reminded that the uses of adversity may be sweet.

As told near the end of the story, Piersall has generously done much in attempting to help others who have had emotional or "fear" problems, through his talks with patient groups in a Chicago organization, "Fight Against Fears." Although he apparently has pride in his over-all success, it seems likely that his experience with illness will prevent the pride from becoming overweening.

VERNON P. WILLIAMS, M.D.

NONCLINICAL NOTES

DR. WILINSKY HONORED

Dr. Charles F. Wilinsky, former executive director of the Beth Israel Hospital and director of the Boston Health Units, has been selected to receive the 1956 Distinguished Service Award of the American Hospital Association. The presentation will be made on September 19 in Chicago at the annual convention of the Association.

INTERNATIONAL RESEARCH COUNCIL

Dr. Hamilton Cameron of New York, himself afflicted with hemiplegia and aphasia since 1943, has announced the incorporation of an International Research Council for the dissemination of knowledge concerning the combined disability. Dr. Cameron may be remembered as having devised, several years ago, an illustrated hand-talking chart, which is distributed free through the headquarters of the Council, 501 West 110th St., New York 25, N. Y.

NOTICES

LAHEY CLINIC FELLOWSHIP LECTURES

The Lahey Clinic Lectures will be given in the Joslin Auditorium, New England Deaconess Hospital, on Wednesday evenings, at 6:00 p.m.

September 19. Bronchogenic Carcinoma. Panel discussion by Carleton Souders, M.D., Magnus I. Smedal, M.D., David P. Boyd, M.D., and William A. Meissner, M.D.

September 26. What the Physician Should Know About Hospitals. James E. Fish, M.D.

Anorectal Disease. Neil W. Swinton, M.D.

October 3. Super Voltage Radiation Therapy: Principles and clinical application. Panel discussion by Ferdinand A. Salzman, M.D., David O. Johnston, M.D., and Richard Granke, B.S.

October 10. Obesity. Rosemary Murphy, M.D.

All members of the medical profession are invited.

OVERHOLT THORACIC CLINIC

A meeting of the Overholt Thoracic Clinic will be held in the Joslin Auditorium of the New England Deaconess Hospital, Boston, on Wednesday, September 19, at 4 p.m.

Dr. Charles P. Bailey will give a talk entitled "Surgery of Aortic Stenosis."

NEW ENGLAND SURGICAL SOCIETY

The annual meeting of the New England Surgical Society will be held at the Poland Spring House, Poland Spring, Maine, on Friday and Saturday, October 5 and 6, 1956.

NEW ENGLAND RHEUMATISM SOCIETY

The fall meeting of the New England Rheumatism Society will be held at the Governor Levi Lincoln House, Sturbridge, Massachusetts, on Friday, October 12, at 3:30 p.m. Dr. Ralph Dorman will speak on the subject "Chemical Configuration of Steroids in Relation to Practical Therapeutic Application."

AMERICAN SOCIETY OF ANESTHESIOLOGISTS

The American Society of Anesthesiologists will hold its annual meeting in Kansas City, October 8-12, 1956.

PAN AMERICAN MEDICAL ASSOCIATION

The Tenth Inter-American Congress of the Pan American Medical Association will be held in Mexico City.

The scientific sessions will be held November 18-22 at 9:00 a.m.

The Congress will be held in sections covering all branches of medicine and surgery. There will be medical moving pictures, panel discussions and scientific and technical exhibits.

Further information may be obtained from Dr. Joseph J. Eller, Executive Director of the Pan American Medical Association, 745 Fifth Avenue, New York 22.

PAN-PACIFIC SURGICAL ASSOCIATION

The Seventh Congress of the Pan-Pacific Surgical Association (president, Dr. Arthur W. Allen, of Boston) will be held in Honolulu, Hawaii, November 14-22.

All physicians are invited to attend. Arrangements should be made as soon as possible so that adequate facilities may be obtained.

Further information may be obtained from Dr. F. J. Pinkerton, Director General of the Pan-Pacific Surgical Association, Room 230, Young Building, Honolulu, Hawaii.

AMERICAN RHINOLOGIC SOCIETY

A symposium on expanding horizons in rhinology sponsored by the American Rhinologic Society will be held in Chicago, October 9-13.

A dinner and evening business meeting will be held in the Illinois Masonic Hospital, 834 Wellington Avenue. On the following three days a clinical program will be held in the Hospital under the direction of the Cottle Fund for Medical Research and Education. Dr. Maurice H. Cottle, Chicago, founder of the Society, will be in charge. The symposium will be held in the Palmer House on October 13.

All members of the profession are invited to attend the scientific sessions as guests of the Society.

Further information may be obtained from Mrs. Mabel Campbell, corresponding secretary, 834 Wellington Avenue, Chicago.

AWARDS IN RADIOLOGIC RESEARCH

The National Academy of Sciences–National Research Council announces that funds for radiologic research are still available from the James Picker Foundation. These consist of grants-in-aid, grants for scholars and fellowships in radiologic research. Applications for the fiscal year 1957-1958 must be submitted on or before December 1, 1956. Further details may be obtained from the Division of Medical Sciences, Room 310, National Academy of Sciences–National Research Council, 2101 Constitution Avenue, N.W., Washington 25, D. C.

SOCIETY MEETINGS AND CONFERENCES

SEPTEMBER 7. First Inter-American Conference on Occupational Medicine and Toxicology. Page 152, issue of July 19.

SEPTEMBER 7–27. Consultation Clinics for Crippled Children in Massachusetts. Page 446, issue of August 30.

SEPTEMBER 8, 9 and 10. Vermont Heart Association and University of Vermont College of Medicine. Page 360, issue of August 16.

SEPTEMBER 9–13. International College of Surgeons. Page 304, issue of August 9.

SEPTEMBER 18. South End Medical Club. Page 402, issue of August 23.

SEPTEMBER 19. Overholt Thoracic Clinic. Page 489.

SEPTEMBER 19 and 20. San Diego Postgraduate Assembly. Page 360, issue of August 16.

SEPTEMBER 19, 26, OCTOBER 3 and 10. Lahey Clinic Fellowship Lectures. Page 489.

SEPTEMBER 27–29. University of Michigan Medical School. Page 402, issue of August 23.

SEPTEMBER 28 and 29. Mississippi Valley Medical Society and American Medical Writers' Association. Page 402, issue of August 23.

OCTOBER 4, 5 and 6. Academy of Psychosomatic Medicine. Page 402, issue of August 23.

OCTOBER 5 and 6. New England Surgical Society. Page 489.

OCTOBER 7, 8 and 9. New Hampshire and Vermont State Medical Societies. Page 304, issue of August 9.

OCTOBER 8–13. International Cancer Cytology Congress. Page 104, issue of July 12.

OCTOBER 12. New England Rheumatism Society. Page 489.

OCTOBER 15–26. New York Academy of Medicine. Page 304, issue of August 9.

OCTOBER 19 and DECEMBER 14, 1956, and FEBRUARY and APRIL, 1957. Massachusetts Society for Research in Psychiatry. Page 56, issue of July 5.

OCTOBER 30 and 31 and NOVEMBER 1. New England Postgraduate Assembly, Boston.

NOVEMBER 12–16. American Public Health Association. Page 402, issue of August 23.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, SEPTEMBER 13

THURSDAY, SEPTEMBER 13

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m. Clinicopathological Conference. Dr. Benjamin Castleman and associates. Pathology Amphitheater, Massachusetts General Hospital.
*12:15–1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.
*3:00 p.m. Thoracic Conference. Case Presentations from the Thoracic Service. Drs. Dwight E. Harken, Harrison Black and Robert F. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
5:00 p.m. Case Presentation and Pathological Discussion Followed by a Subject of Special Presentation. Joslin Auditorium, New England Deaconess Hospital.

FRIDAY, SEPTEMBER 14

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Medical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*12:00 m. Pediatric Grand Rounds. Thorndike Amphitheater, Boston City Hospital.
*12:30–1:30 p.m. Surgical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*2:00–3:00 p.m. Pathology Conference. Dr. James Graham. Saint Elizabeth's Hospital.
*4:00–6:00 p.m. X-Ray Conference. Dr. Merrill Sosman. Stearns Auditorium, New England Center Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.
*4:30 p.m. Neuroradiologic Conference. X-Ray Conference Room, New England Deaconess Hospital.

SATURDAY, SEPTEMBER 15

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*8:30–10:00 a.m. Surgical Grand Rounds. Drs. Charles G. Child, III, A. J. A. Campbell and staff. First (Tufts) Surgical Service, New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*9:00–10:00 a.m. Anesthesiology Conference. Dr. Benjamin Etsten. Anesthesia Laboratory, New England Center Hospital.
*9:30–11:00 a.m. Surgical House Officers' Conference. Second-Floor Conference Room, Carney Hospital, Dorchester.
*10:30 a.m. Teaching Ward Rounds. Ward South 2, Free Hospital for Women.

(Concluded on page xxix)